

Coordination impairment between the somatic and parasympathetic nervous system divisions in the human sacral micturition centre following spinal cord injury

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Abstract

The detrusor-sphincteric dyssynergia is analyzed by comparing the natural impulse patterns of secondary muscle spindle afferents (SP2) contributing to continence (SP2 fibre activity changes are similar to detrusor pressure changes) and sphincteric motoneurons in a brain-dead human with those in patients with spinal cord injuries. In the brain-dead the sphincteric motoneurons, subserving continence, were inhibited at a time, when preganglionic parasympathetic efferents and a SP2 fibre increased their activity (physiologic). In paraplegics the sphincteric motoneurons were not inhibited (pathophysiologic). In the brain-dead, an SP2 fibre showed doublet firing (interspike interval (II) 10 to 14 ms) for low level parasympathetic activation and multi-ending regular firing for high parasympathetic activation. In one paraplegic with strong bladder dysfunction, the multi-ending regular firing was replaced by a repeated burst firing with a shortest II of 0.2 ms (transmission frequency = 5000 Hz). The pathologic firing patterns of the SP2 fibres, the detrusor-sphincteric dyscoordination, and hyperreflexia in paraplegics are most likely a result of neuronal network changes in the parasympathetic and somatic nervous system divisions of the sacral micturition center after spinal cord injury. It is discussed that urinary bladder functions can be re-learned.

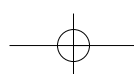
Data Summary

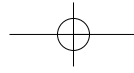
1. Humans with spinal cord injury often show detrusor-sphincteric dyssynergia of the urinary bladder. The somatic external bladder sphincter is activated at the same time as the detrusor (smooth muscle) with the consequence that the urinary bladder cannot be emptied. This dyscoordination between the somatic and parasympathetic nervous system divisions in the human sacral micturition centre is reflected urodynamically in the simultaneous increase of the detrusor pressure and the electromyographic activity of the pelvic floor.

2. The time course of the increase in the secondary muscle spindle afferent activity, induced by the parasympathetic nervous system in muscle spindles contributing to continence, is very similar to that of detrusor pressure. The detrusor-sphincteric dyssynergia is therefore analyzed by comparing the natural impulse patterns of single secondary muscle spindle afferents (SP2) and sphincteric motoneurons in a brain-dead human (physiologic) with those in patients with spinal cord injury (pathologic). The parasympathetic nervous system was activated by painful bladder catheter pulling.

3. In a brain-dead human the sphincteric motoneurons subserving continence were inhibited at a time, when preganglionic parasympathetic efferents increased their activity (physiologic) for 10 s and an SP2 fibre increased its activity for several minutes. In a paraplegic with a strong bladder dysfunction, the SP2 fibre activity increased, due to parasympathetic activation, lasted for approx. one minute, showed undulations, and its amplitude was smaller than that measured in a brain-dead human. The sphincteric motoneurons were not inhibited (pathologic).

4. In the brain-dead human, an SP2 fibre showed doublet firing (probably physiologic) with interspike intervals (IIs) of duration between 10 and 14 ms for low level parasympathetic activation. For high level parasymp-





pathetic activation this single parent spindle afferent fibre showed multi-ending regular firing of up to 6 endings (probably physiologic) with IIs of a duration of predominantly 15 to 25 ms. In one paraplegic with a strong bladder dysfunction the doublet firing was less regular, even though two II peaks at 10.2 and 11.2 ms occurred in a II distribution similarly as in the brain-dead human. The multi-ending regular firing was replaced by a repeated burst firing (probably pathologic). In a second paraplegic with strong detrusor-sphincteric dyssynergia the burst firing consisted of up to 6 impulses with increasing IIs and a first II of approx. 0.2 ms (transmission frequency = 5000 Hz.). In a third paraplegic with a less strong dysfunction of the bladder a highly activated SP2 fibre showed an activity pattern intermediate to those of multi-ending regular firing and burst firing. The doublet and multi-ending regular firing of parasympathetically innervated muscle spindles may represent messenger function, which becomes impaired following spinal cord injury.

5. The time constant for the activity decrease of a spindle afferent fibre following parasympathetic activation was 31 s in a paraplegic and approx. 40 s in a brain-dead human. It is concluded that the muscle spindles are unchanged following spinal cord injury. The pathologic firing patterns of the SP2 fibres are thus probably a result of neuronal network changes in the parasympathetic and somatic nervous system divisions of the sacral micturition center.

Key-words: Human – Brain-dead – Spinal cord injury – Urinary bladder – Continence – Urodynamics – Sacral micturition centre – Natural impulse patterns – Single-fibre action potentials – Fusimotor activity – Spindle afferent activity – Doublet firing – Messenger function – Parasympathetic activity – Sphincteric motoneuron activity – Detrusor-sphincteric dyssynergia – Coordination dynamics therapy – Stem cell therapy

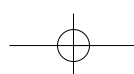
Introduction

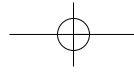
The goal of this current research is to cure spinal cord injury in general and urinary bladder functions in particular. After having shown in a previous publication that the identification of somatic and parasympathetic nerve fibres by the group conduction velocity and the group nerve fibre diameter had not changed following spinal cord injury, it will be analyzed in this article, on the basis of natural impulse patterns, traveling into and out of the sacral micturition centre, what became pathologic in the organization of the central nervous system (CNS) following spinal cord injury with the goal in mind to develop cure.

Normal voiding is a voluntary act which results in sustained contraction of the bladder (detrusor) and relaxation of the urethra until the bladder is empty. To enable fluid flow along the urethra it is necessary that the pressure in the urinary bladder exceeds that within the urethra lumen. Under normal circumstances, in order to initiate micturition, a fall in urethral pressure immediately precedes a rise in pressure within the lumen of the bladder (Fig. 11.13 in (70)). Usually this pressure rise is produced by active contraction of detrusor smooth mus-

cle at the onset of micturition. The extensive vesical part of the pelvic plexus and the profuse distribution of autonomic motor nerves emphasize the importance of the autonomic nervous system in initiating and sustaining bladder contraction during micturition. Immediately prior to the onset of micturition, the tonus of the striated external bladder sphincter (rhabdosphincter) is reduced by central inhibition of its somatic motor neurons located in the third, fourth and fifth sacral spinal segments. This inhibition is mediated by descending spinal pathways originating in higher centers of the central nervous system (CNS) (70). The central integration of the nervous control of the bladder and urethra is essential for normal micturition.

Immediately following complete spinal cord injury there is a period of spinal shock that lasts about 3 weeks or longer. This period is characterized by muscular flaccidity and a loss of spinal reflexes. The recovery of reflex activities below the level of the injury occurs at different times. If bladder reflexes reappear they differ in some important respects from those in a normal individual. The 'autonomic bladder' contracts in response to distension, but the power is rarely that of the normal bladder, and the residual volume increases. Lesions





above the level of the brain stem centers lead to involuntary voiding that is coordinated with sphincter relaxation (detrusor-sphincteric synergy). Lesions below the level of the brain stem centers but above the lumbosacral spinal cord lead, after a period of bladder paralysis associated with spinal shock, to involuntary reflex voiding that is not coordinated with sphincter relaxation (detrusor-sphincteric dyssynergia) (Fig. 11.2 of (70)). In this paper the coordination between the detrusor and the external bladder sphincter will be compared between paraplegic patients with lesions below the brain stem and detrusor-sphincteric dyssynergia (pathologic) and a brain-dead human with an at least partly destroyed brain stem and an at least partial detrusor-sphincteric synergy (partial physiologic).

If the spinal cord injury is complete it is believed that paraplegics develop vesicosphincteric dyssynergia because of the disconnection from the pontine micturition center which is responsible for the coordination of the detrusor and the external bladder sphincter (see above). In cases in which no detrusor-sphincteric dysynergia has developed, the spinal cord injury is believed to be incomplete, so that supra-spinal centers can still coordinate bladder functions. The external bladder sphincter will not be 'coactivated' with the detrusor in response to distension. The view that the important function of coordination is performed by spino-bulbo-spinal pathways has incorporated anatomical ideas of a hierarchy of functions of increasing complexity, the further rostrally one goes in the CNS. Still, the coordination for the mutual inhibition of detrusor and external bladder sphincter may be located in the sacral micturition center. In this and the following three papers (84-86) I shall try to shed further light onto this dyscoordination problem, using the single-nerve fibre action potential (AP) recording method.

On the basis of such better electrophysiological understanding of human urinary bladder functions, a non-destructive learning-based movement therapy is developed to cure urinary bladder functions by using additionally knowledge of the integrative functions of the human CNS (78,81) and learning transfer from special coordinated movements to urinary bladder functions (85). It will be shown that such learning transfer is successful in repairing urinary bladder function (86), since the somatic and the autonomic divisions dovetail with one another with

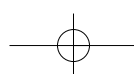
respect to those special movements and urinary bladder functions (84-86). The necessary connection to the pontine micturition center for the coordination control of the detrusor and the external bladder sphincter is achieved by limited regeneration of the human spinal cord (82,86) upon coordination dynamics therapy (81,82).

Functions of the CNS can be understood based on two important concepts, one old, another one new. The first is the evolutionary principle of levels of function, which implies that rostral segments of the brain have become dominant over caudal, and that when higher parts are removed many activities of lower segments are, after a time, 'released' and can then be more readily analyzed (19).

The second, and a newer, concept relates to the extensive interaction normally occurring between somatic and autonomic reflexes. The autonomic division of the nervous system can no longer be regarded as a purely peripheral system, but rather as an elaborately organized division of the CNS with representations at all levels. At each level, moreover, the somatic and the autonomic systems dovetail with one another (19).

For animals, reviews by de Groat (13) and de Groat et al. (15,16) provide a basis for understanding how the filling and voiding functions of the bladder work. de Groat (13) states that the primary stimulus for micturition is bladder distension, which induces reflex activation of the parasympathetic excitatory outflow to the bladder, depression of the sympathetic inhibitory outflow, and depression of the somatic efferent output to the external sphincter; secondary reflexes elicited by the passage of urine through the urethra may reinforce these primary reflexes and facilitate the complex emptying of the bladder. When the micturition reflex is exceeded, the parasympathetic reflex pathway through the brain stem is active. McMahon and Morrison (30-33,36) used a similar approach, but attempted to separate functional pathways concerned with the reflex pathways and with the control of micturition threshold. For an introduction to the physiology of the lower urinary tract, see (70).

Yates (74) has constructively criticized the quality of research in the area of human urinary bladder physiology. In particular, he has recommended that investigators should look at the methods being used in parallel disciplines.



On the basis of a newly developed basic human electroneurophysiologic method, the recording of single-nerve fibre action potentials (APs), a classification scheme of the human peripheral nervous system has been developed (44,46,48), which still holds in paraplegics (58,83). Since it is possible to simultaneously identify impulse patterns of single afferent and efferent nerve fibres (Fig. 1), functions of the human CNS can be analyzed. The power of the method lies in the existence of a unique anatomical situation in humans: because of the ascensus of the human spinal cord, and as humans have no tails, urinary bladder functions are nearly purely represented in thin long, mainly S3 and S4, nerve roots. Because of the missing of epineurium and perineurium (apart from a thin layer of cells) single-nerve fibre APs can be ideally recorded.

Human lower urinary tract physiology and pathophysiology will be investigated with this electrophysiological method by comparing the measurements obtained from paraplegics with detrusor-sphincteric dyssynergia of the urinary bladder with those of a brain-dead human (HT6). The starting point will be routinely performed clinical urodynamic investigations.

Method

Measurements were performed in 9 patients with spinal cord injury (paraplegics), dyssynergia of the urinary bladder, spastic pelvic floor and spasticity in general. Only those patients have been selected for demonstration who showed the properties (impulse patterns) of interest for the present investigations. The electrophysiological data obtained from a brain-dead human (HT6) were taken from previous analyses (54-56), in a few cases the original data were reevaluated. The ethical aspect of performing electrophysiologic measurements in patients is that the method of recording single-nerve fibre action potentials (APs) was primarily used for diagnosis during the surgery and research was performed simultaneously. Actually, a close correlation between diagnosis and research measurements can be expected to bring progress into human physiology and pathophysiology. A close cooperation between clinic and research will be in the best interests of the patients in the long-term prospect.

Electrophysiology

Single-nerve fibre APs were recorded extracellularly from nerve roots with 2 pairs of platinum wire electrodes (electrode pair distance = 10 mm; electrode distance in each pair = 4 mm) at 2 sites, preamplified ($\times 1000$), filtered (passing frequency range 100 Hz-10kHz) and displayed on a digital storage oscilloscope and also stored on a video tape using a PCM-processor and a video recorder (see also (58,83)). Trace 'a' was the recording from the proximal electrode pair, and trace 'b' from the distal pair. Conduction velocities of single fibres were calculated from the conduction distance (electrode pair distance = 10 mm) and the respective conduction times, the time needed for an AP to cover the conduction distance (time difference between traces 'a' and 'b' for a particular AP). APs from afferent and efferent fibres could clearly be distinguished since for the used electrode arrangements (differential electrodes), the main phase (second phase) from afferent fibres is upwards and that of efferent fibres downwards. Since the afferent and efferent APs reach the electrode pair from opposite directions, also the conduction times of afferent and efferent APs are opposite. The conduction velocities of afferent and efferent nerve fibres were plotted in velocity distribution histograms for afferent and efferent fibres. The nerve groups of afferent and efferent fibres were identified by the peaks and the ranges in the distributions and by the calibration relation (e.g., α_2 -motoneurons conduct with the same velocity as do the secondary muscle spindle afferent fibres). The single-fibre APs of the multi-fibre recordings were then identified by the conduction velocity and assigned to their respective nerve fibre group (Fig. 4). The extraction of single-fibre impulse patterns from a multi-fibre recording from a whole nerve root is performed using conduction time and AP wave form comparisons and reoccurring AP patterns (Fig. 1). Different temperatures of the nerve roots do not change the patterns. A human ventral S4 root contains approx. 300 fibres with a diameter range down to 3 to 4 μm (Fig. 5 and Table 1 of (58)). In a certain recording situation may only be 5 to 50 fibres active. In general, the recording conditions have to be arranged so that the activity is not too high. The best approach under physiologic conditions is mostly to analyse motoneurons in the dorsal roots and affer-

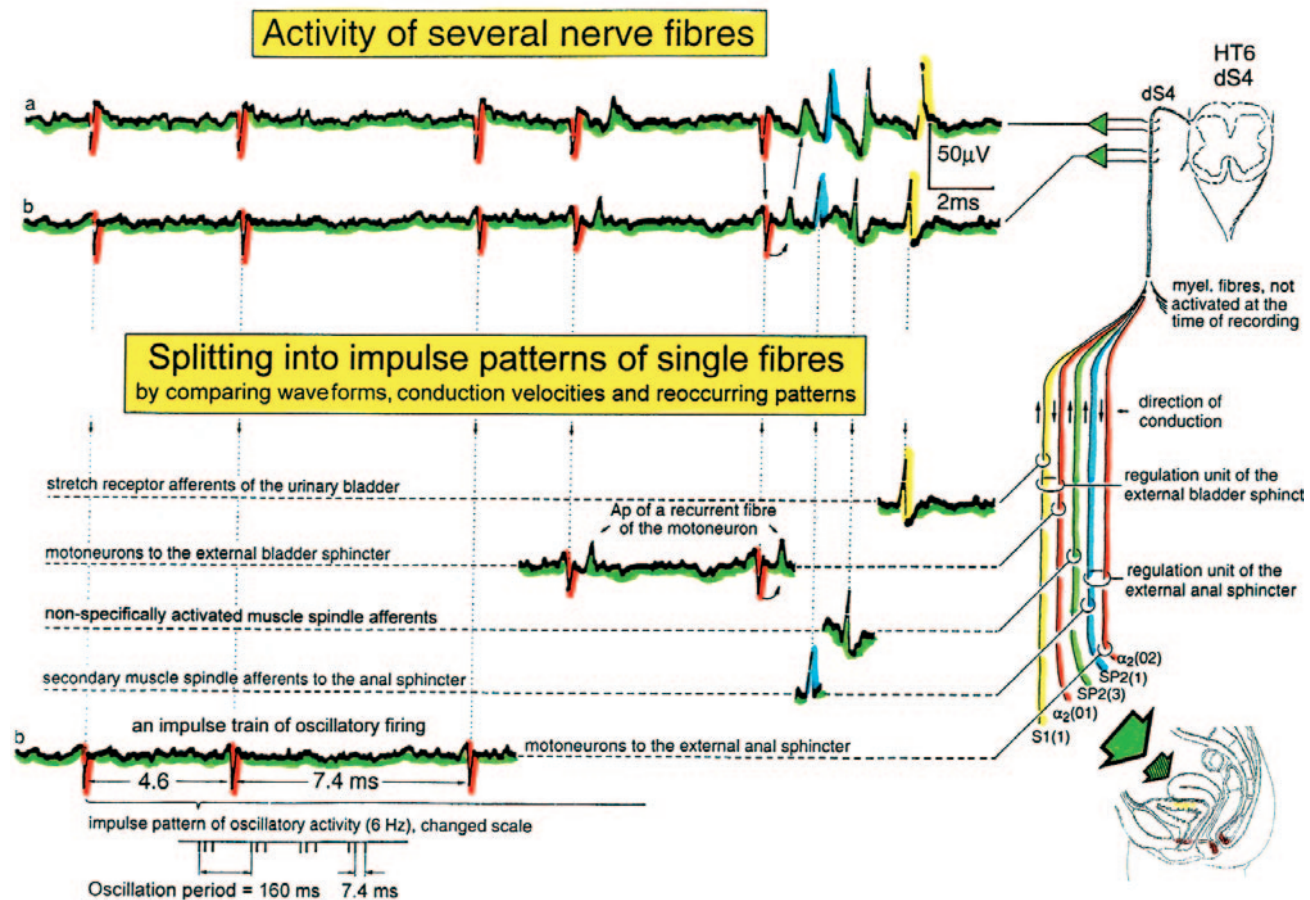
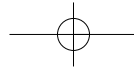
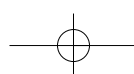


Fig. 1. – Schematic splitting of the activity of several nerve fibres into simultaneous impulse patterns of single fibres by comparing wave forms, conduction velocities and reoccurring characteristic impulse patterns (rhythmic firing of sphincteric motoneurons). The different conduction times and wave forms were recognized on an expanded time scale. “*” see Fig. 10. of (59) for receptor sites and the location of the muscles which are innervated by the sphincteric motoneurons. Stretch receptor and secondary muscle spindle afferents contribute to the drive of sphincteric motoneurons and form, together with other afferents, regulation units.

ent fibres in the ventral (motor) roots. Actually, the success of the method lies in the violation of the Dales principle. E.g., touching with a finger the S4 dermatome evokes a high transient skin afferent activity in the ipsilateral dorsal S4 root, so that nearly no single-nerve fibre APs can be recognized any more. Upon pin-pricking the coccygeal dermatome and recording from the coccygeal root on that side, excellent recordings can be obtained (46,52). The members of the operating theatre were advised not to touch the patient or the covering towels to avoid response from the afferent and efferent fibres. Under pathophysiologic conditions it may be difficult to obtain suitable low activity level recordings from lower sacral nerve roots. The afferent fibres of a ventral S3 or S4 root may fire with such a high

activity that the APs of the afferent fibres cover the APs of the efferent fibres (cf. Fig. 11e and Fig. 11f). When retrieving signals from the tape after the surgery, it is looked for good pieces of recording (high AP amplitude, low activity, few artifacts, not too low a temperature). Sweep pieces of 0.4 and 0.8 s were fed from the tape to the oscilloscope and analyzed there. The APs from several single fibres are recognized by their shape on trace ‘a’ and trace ‘b’ and the conduction times. By passing the window of the scope (0.5 to 2 ms/cm) through a 0.8 s sweep, the times of the occurrence of single-nerve fibre APs (Fig. 4) are written down from the memory address of the scope. Simultaneous impulse patterns of afferent and efferent fibres are then drawn (e.g. Fig. 8A,D). The calculation of interspike intervals



(IIs) and II distribution histograms from the occurrence time data is easy. Also, activity levels can be easily constructed. The problem lies in the recognition of all APs from a particular fibre to obtain their times of occurrence. Often, the AP wave forms of several fibres are unique, and then comparably easy simultaneous impulse patterns can be constructed if the visual memory of the researcher is good. However, also often the AP wave forms of several fibres are rather similar on both traces as are the conduction times, especially because the digitization is mostly too poor (at least 5 digitization points per AP) to get a long sweep into the scope. The knowledge of impulse patterns will help because it can partly be predicted when a particular fibre will fire again. For example, an α_2 -motoneuron firing with an impulse train of 3 APs in the oscillatory firing mode will on average fire again with a 3 AP impulse train after 160 ms; thus, there is a high probability that the next firing occurs at that point. The procedure used for the analysis is the following if one has e.g. 3 fibres from which APs can be recognized. By passing the window through a 0.8 s sweep, the times of occurrence (memory address, cursor) are written down. If an AP wave form can only be identified with doubt or can be mixed up with those of another fibre, the situation is noted. Then, the impulse patterns of the 3 fibres of the 0.8 s sweep are plotted. With the additional information of impulse patterns, and taking into account algebraic adding of potential changes of different APs and of noise and artifact potentials, the majority of doubtful AP waves can successfully be identified. If an important point cannot be identified, that particular sweep has to be omitted and another one taken from the tape. It is always good to have several stimulations of the same kind on the tape. Immediate plotting with a following reinspection of the doubtful cases is very efficient. It should not be concluded that the construction of impulse patterns is a speculation. Sometimes there are only two motoneurons in a dorsal root (2 thick dorsal root efferents) or one or two thick afferent fibres in a ventral root, so that their impulse patterns are obvious. In detail, thick fibres (fast conducting) generate APs of large amplitude, thin fibres (slowly conducting) of small amplitude (43,58,83). The APs of unmyelinated fibres are normally not visible. The APs of a ventral root afferent fibre can be distinguished from the APs of the ventral root

efferents by the opposite AP amplitude and conduction time. Often the activity of the motoneurons is low, so that the impulse pattern of a single thick ventral root afferent fibre (multi-unit impulse pattern) is close to a single-unit impulse pattern. Because of the importance it was always tried to get as much out of the recordings as possible. Each good recording is a small treasure. Since the brain of the researcher has to 'store' the AP contours of several fibres (besides drawing them down) including their variations, the time basis should not be changed during the analysis. If fast (short AP duration) and slowly conducting fibres (long AP duration) are included in the identification, a sweep has to be inspected two times. The first time with the normal time base to recognize the fast potentials, and a second time with a compressed time base to better recognize the slowly conducting fibres with a long AP duration, such as preganglionic parasympathetic neurons.

Urodynamic measurements

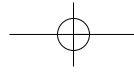
The electromyographic recordings with surface electrodes from the pelvic floor, and the bladder and rectal pressure measurements were performed with the cystometry apparatus Dantec UD5500.

Results

Single-nerve fibre action potentials (APs) were recorded extracellularly in 3 paraplegics during the implantation of an electrical anterior root stimulator for bladder control. Interspike intervals were calculated, impulse patterns constructed and activity levels compared with urodynamic parameters measured pre-operatively.

Dyssynergia of the urinary bladder

In Fig. 2 typical detrusor-sphincteric dyssynergia of the urinary bladder is demonstrated, in a patient with a spinal cord injury sub TH12 present for 2 years. Because of a malformation of the ureters and ureteric reflux, this patient underwent surgery for the implantation of a sacral anterior root stimulator (9). Without the malformation the bladder dysfunc-



Standard urodynamic recordings before operation, Para 5

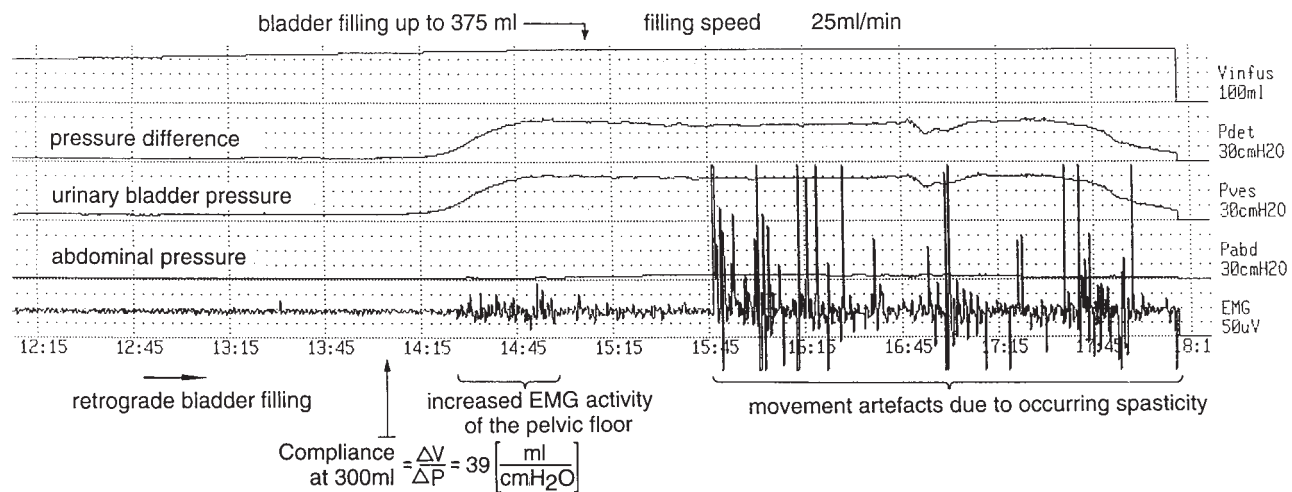


Fig. 2. – Standard urodynamic recording including intravesical pressure (urinary bladder pressure), abdominal pressure, detrusor pressure (pressure difference) and pelvic floor electromyography (EMG). Detrusor pressure is that proportion of the intravesical pressure which is produced by active and passive bladder wall properties. Detrusor pressure is calculated by electronically subtracting the value of abdominal pressure from that of intravesical pressure. This derivation is extremely important in order to be able to distinguish intrinsic and extrinsic contributions to intravesical pressure. Upon retrograde bladder filling the detrusor started to contract at approx. 350 ml. Abdominal pressure is the pressure around the bladder and this is measured as rectal pressure.

tion would have still been tolerable (see later). Upon retrograde bladder filling the intravesical pressure increased. At a filling volume of 350 ml the detrusor contracted automatically in response to bladder distension. The electromyographic (EMG) activity of the pelvic floor increased at a time when the detrusor pressure increased. If the external anal and the external (striated) bladder sphincters were activated at the same time, and this probably was the case, then the external bladder was activated at approximately the same time as the detrusor. This coactivation is called detrusor-sphincteric dyssynergia of the bladder, since in normal humans the external bladder sphincter is relaxed (inhibited) upon the activation of the detrusor, so that urine can pass through the urethra under low pressure.

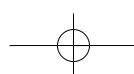
The loss of sphincteric relaxation during detrusor contraction results in a high bladder pressure during voiding. A high bladder pressure will result in a detrusor hypertrophy with an increased bladder stiffness, as estimated from a reduced compliance (and, possibly, an increased bladder infection rate (65); in addition, there probably will be an increase of stretch (S1) and tension (ST) (83) and pain receptor afferent activity of the bladder wall (70) result-

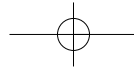
ing in a too early activation of the detrusor in response to it (59,84). The storage capacity of the bladder may thus become reduced to 50 ml or even less. On the other hand, the intravesical pressure may cause ureteric reflux, and due to infections, progressive renal impairment.

Upon further filling of the bladder (Fig. 2) and a stoppage of the filling, movement artifacts indicate the occurrence of spasticity of the lower body. The avoidance of the seeming coactivation of the detrusor, the pelvic floor and the striated bladder sphincter is an important clinical problem (continence) as well as an interesting scientific problem. Since it is highly unlikely that parasympathetic motoneurons activate besides the detrusor (smooth muscle) also the external bladder sphincter (striated muscle), the problem lies in the pathologic coordination between the parasympathetic and the somatic nervous systems.

Doublet and burst firing of secondary muscle spindle afferents (SP2) in paraplegics

I shall now try to show with the use of electrophysiological data that some muscle spindles in the





lower sacral range, in the domain of the sacral parasympathetic nervous system, are innervated by parasympathetic efferent fibres. The response of SP2 fibres to the probable parasympathetic activation is a doublet and burst-like firing with short interspike intervals (IIs). Primary muscle spindle afferents are only seldom found in the lower sacral range.

Fig. 3a,b shows the APs of an SP2 fibre with the second main phase of a triphasic AP upwards (accor-

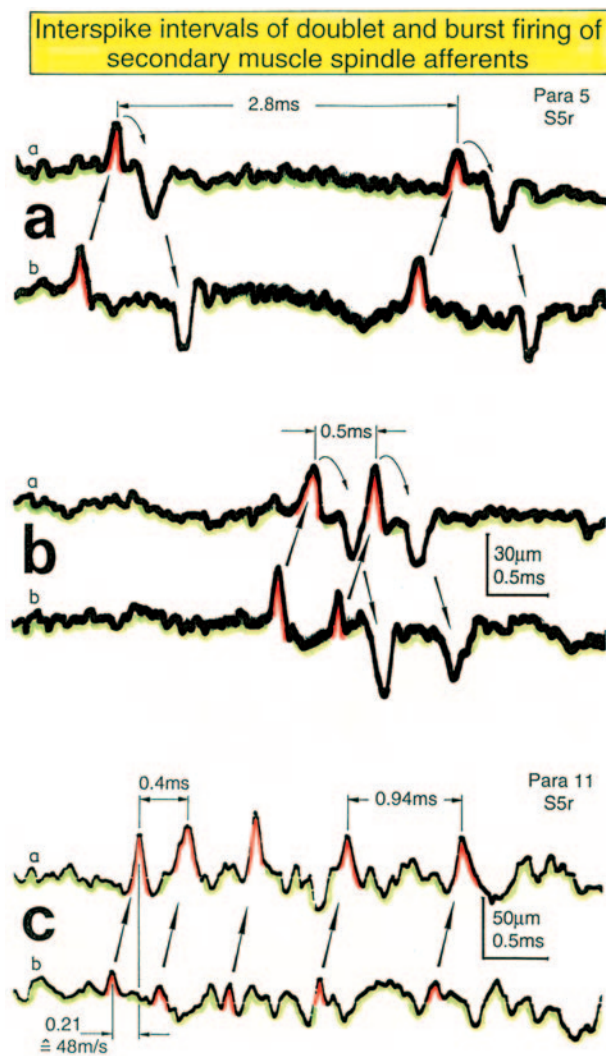


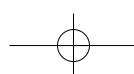
Fig. 3. – Doublet and burst firing of secondary muscle spindle afferent fibres. Recording a, b, paraplegic 5, and c, paraplegic 11. Interspike intervals (IIs) are indicated. In 'c' the single afferent fibre conducted at 48 m/s, and II increased from 0.4 to 0.94 ms. The single-spindle afferent fibre in 'a' and 'b' is uniquely marked by performing a loop which is demonstrated by an efferent-like AP time-locked to the afferent AP (see also Fig. 12). The AP (action potential) amplitude calibration 1μm designates microvolt (μV).

ding to the electrode arrangement). Since most likely, this afferent fibre performed a loop in the root (see also Fig. 12), the APs of this fibre were uniquely marked by the efferent-like AP of the backward running fibre. In Fig. 3a the II between two APs of that secondary fibre is 2.8 ms. In Fig. 3b the II of 0.5 ms is even shorter (transmission frequency = 2000 Hz). In Fig. 3c the activity of another SP2 fibre in another paraplegic is shown. Those APs occur in a burst-like pattern with IIs increasing from 0.4 ms to 0.94 ms. The II of 0.4 ms represents a transmission frequency of 2500 Hz.

A systematic analysis of doublet (Fig. 3a,b), burst (Fig. 3c) and continuously short II firing of SP2 fibres will now be used to measure parasympathetic muscle spindle activation and to clarify, by direct comparison with the impulse patterns observed in a brain-dead human, whether such parasympathetic activation patterns are physiologic or pathophysiological.

Fig. 4A,B shows two doublet APs of a secondary muscle spindle afferent fibre SP2(1) of paraplegic 9, with IIs of 11.6 and 18.2 ms. In Fig. 4C,D,E typical AP wave forms (templates) of an SP2(2) fibre, α_2 , α_3 and γ_1 -motoneurons, are given; their impulse patterns will be followed up continuously over several seconds to analyse continence functions of the human nervous system.

The activity level of the SP2(1) fibre in paraplegic 9 is shown in Fig. 5A in dependence on time. Following anal and bladder catheter pulling and other natural stimulations the SP2(1) fibre increased and/or decreased its activity. The trace of the activity changes shows several peaks. Especially the bladder catheter pulling induced large peaks in the activity level. It is known that in paraplegic's strong bladder catheter pulling activates the detrusor to contract. The activity peaks may therefore be due to parasympathetic muscle spindle activation, and they are marked with 1, 2, 3 and 4. A better justification for the probable parasympathetic activation will be given below. Since in an earlier publication it was suggested that the doublet firing can be attributed to low level parasympathetic muscle spindle activation (54,56), in Fig. 5A also the doublet activity level (doublet II < 40 ms) has been drawn. Also the doublet activity was highest following bladder catheter pulling in parallel with the occurrence of the activity peaks. To analyse the patterns of the doublet fir-



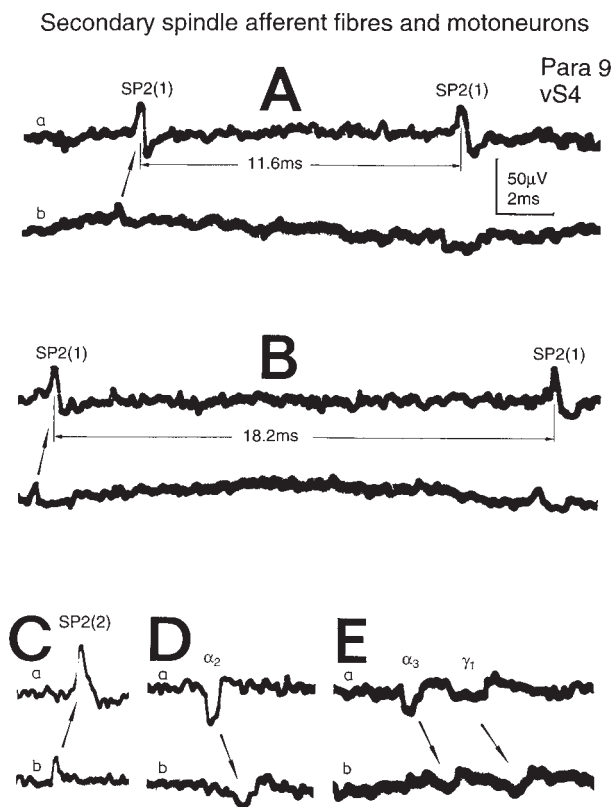
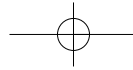


Fig. 4. – Characteristic wave forms of extracellular action potentials of secondary muscle spindle afferent fibres (SP2(1), SP2(2)), α -motoneurons (α_2 , α_3) and a dynamic fusimotor (γ_1) used to construct single-fibre impulse patterns. Two doublet interspike intervals (DIIs) of 11.6 ms (A) and 18.2 ms (B) are indicated. Paraplegic 9, nerve root vS4.

ing, doublet II frequency distribution histograms have been plotted for different time intervals (Fig. 5Ba-h). To reveal signs of pathology in these patterns, the doublet firing histogram and the histogram for the multi-ending regular firing obtained from brain-dead human HT6 are given in Fig. 5C.

Comparison of doublet and burst firing of paraplegics with doublet and multi-ending regular firing of a brain-dead human

In the brain-dead human HT6, the most likely physiologic firing pattern of the secondary spindle afferent fibre SP2(2) (Fig. 5C) following parasympathetic activation included the doublet firing, the 2 plus 3 ending firing, and the 4, 5 or 6 multi-ending regular firing (54,56). The doublet firing, of most

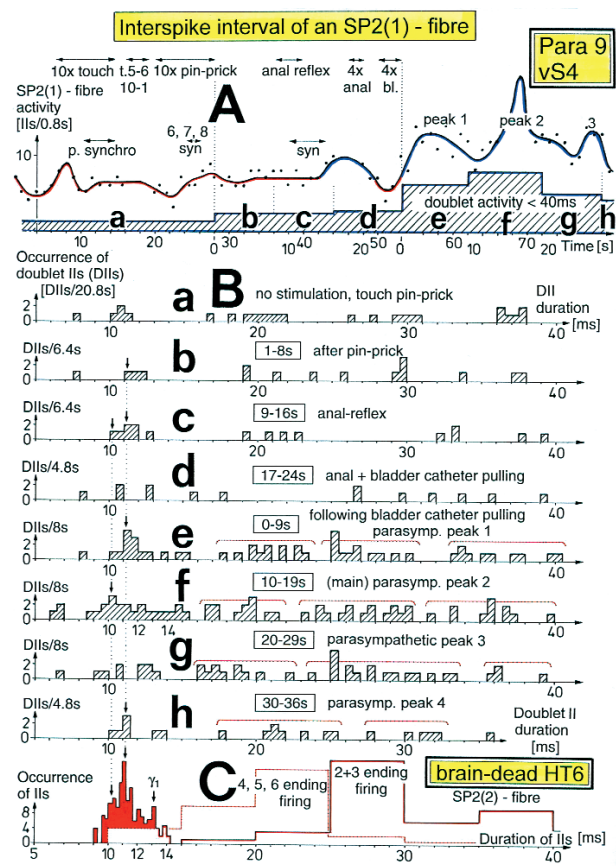
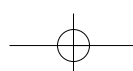
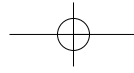


Fig. 5. – A. Activity of a secondary muscle spindle afferent fibre SP2(1) in dependence on time (interspike intervals = IIs = (APs – 1)/0.8 s). 4x anal = Fourfold anal catheter pulling; 4xbl. = Fourfold bladder catheter pulling; t.5-6,10-1 = short anal reflex stimulation; syn = synchronization of oscillators, not under consideration here. peak 1, peak 2, 3 = activity peaks of SP2(1) fibre (as will be shown, they are peaks of parasympathetic activity increase). The cross-hatched histogram with histogram classes a-h is a histogram of doublet activity; doublet activity < 40 ms = activity of doublets with interspike intervals (doublet interspike intervals = DIIs) < 40 ms. Note the strong increase in doublet activity following bladder catheter pulling. B. Interspike interval (DII and burst interspike interval) distribution for the time intervals a-h. The arrows at 10.2 ms and 11.2 ms indicate peaks of DIIs similar to those measured in HT6 (C). The dotted parenthesis indicate possible grouping of IIs during burst firing, in similarity to the multi-ending regular firing observed in brain-dead human HT6. C. DIIs and multi-ending regular firing observed in brain-dead human HT6 (54) shown for comparison. Direct comparison is indicated by double framing of para 9 and HT6.

likely two encoding sites of the parent SP2(2) fibre in HT6 (54), shows 3 peaks at 10.2 ms, 11.2, and 13.1 ms. The doublet duration peak at 13.1 ms is marked γ_1 , indicating that a γ_1 -fusimotor fibre in the





HT6 also had a doublet histogram peak at that value (56), supposing that this peak occurred because of the γ_1 -fusimotor activity or that the γ_1 neuronal network was controlled also by the parasympathetic division. Anyhow, this HT6 peak cannot be found in the doublet firing of the SP2(1) fibre in paraplegic 9 (Fig. 5B). The other two doublet peaks firing at 10.2 and 11.2 ms can be seen in the SP2(1) fibre doublet histogram of Fig. 5B. The general difference in the doublet firing of the SP2 fibres between the paraplegic and the brain-dead human is that the doublet firing histogram for paraplegic 9 is more broadened, in particular in the direction of short IIs. Since human secondary spindle afferents outside the sacral parasympathetic domain do not fire with IIs shorter than 50 ms (72), it was argued that the doublet firing stems from 2 endings (encoding sites) of a parent spindle afferent fibre, which are coordinated by the parasympathetic division in the way that a second ending fires with a delay of 10 to 14 ms (54,56). In paraplegic 9, the doublet histograms show a more broadened distribution. Thus, the coordination of the firing of 2 encoding sites of the secondary spindle afferent fibre is partly lost. It remains unclear, whether the coordination of the two encoding sites by the parasympathetic division occurs directly at the muscle spindle level or via the fusimotor system.

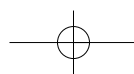
For high level parasympathetic activation the secondary spindle afferent fibre in HT6 fired with equidistant impulses of up to 6 endings of the parent fibre. Again, the parasympathetic division probably coordinated up to 6 encoding sites to fire with equidistant APs. Only when a new encoding site was recruited with the increasing activity, the firing became transiently irregular for some time (see Fig. 9B (55 s)). This regular firing with equidistant APs was lost in paraplegic 9. Instead, the parasympathetically induced spindle afferent activity involved bursts with increasing II duration. The bursts consisted of up to 6 APs indicating a sudden activation of up to 6 encoding sites of the parent secondary spindle afferent fibre (see Fig. 3C and Fig. 11d,e). In Fig. 5Be,f,g,h the multi-ending firing histograms for paraplegic 9 show grouping (indicated by the dotted parenthesis). This grouping may suggest preforms or rudiments of multi-ending regular firing. Directly plotted impulse patterns will later show more clearly the differences between physiologic and pathophysiologic activation.

In any case, natural stimulation of the parasympathetic division in paraplegics, induced by anal and bladder catheter pulling, resulted in doublet firing of 2 endings and multi-ending firing of 3 and more endings. The regularity of firing (the specificity of firing), observed in HT6, was lost in the paraplegics. The physiologic specific doublet and equidistant AP firing (HT6, multi-ending regular firing, probably physiologic) changed into pathologic less specific doublet, burst, and non-equidistant AP firing (paraplegics, less regular firing, pathologic), which may indicate a loss of coordinated firing of parasympathetic neurons, innervating the muscle spindle. In the following section it will be shown that parasympathetically induced muscle spindle activation is actually connected to the activation of the parasympathetic division and, most likely, does not originate from the somatic nervous system.

Time course comparison between the proposed parasympathetically induced muscle spindle afferent activity and the detrusor pressure

Upon retrograde bladder filling in patients with complete spinal cord injuries, the detrusor was reflexly activated at rather small storage volumes, as could be measured urodynamically by the detrusor pressure. In paraplegic 5, the detrusor was automatically activated at a bladder filling volume of approx. 350 ml (Fig. 2), and in paraplegic 9 at approx. 10 ml (!). Reasons for too small storage volumes were given in the previous paper with the increased afferent input from the bladder and strong dysorganization of the neuronal networks in the spinal cord (83). It was found there for the paraplegics 7 and 11 that the first high bladder afferent activity occurred at bladder filling volumes in the operation, at which the detrusor was activated pre-operatively. In para 7 the first high afferent input occurred at a filling volume of 150 ml; the detrusor was activated at 160 ml (Fig. 8 of (83)). In para 11 the first comparatively high afferent input occurred at 50 ml filling volume; the detrusor was activated at 80 ml.

During surgery under light anesthesia the detrusor never responded to the filling of the bladder in 120 patients. Also, quick filling with 4°C saline solution did not activate the parasympathetic division. Only in one instance, during surgery on a tetraplegic



Parasympathetic muscle spindle activation in comparison to urinary bladder pressure

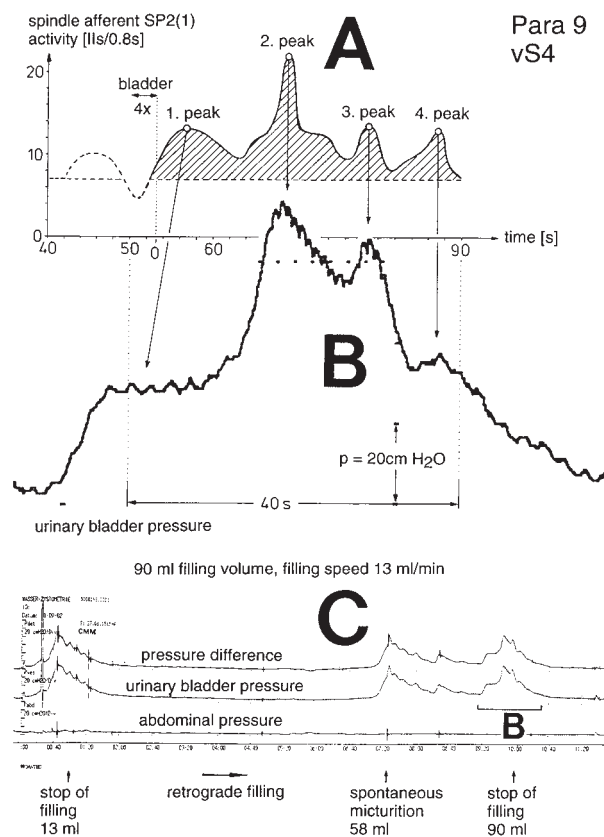


Fig. 6. – Comparison between changes in secondary muscle spindle afferent activity and detrusor pressure (measured before the surgery; for the implantation of a sacral anterior root stimulator). Paraplegic 9.

A. Activity changes of the afferent fibre SP2(1) from Fig. 5 following bladder catheter pulling. Approx. mean activity level is represented by a dashed line at 7.5 IIs/0.8 s ((APs -1)/0.8 s). The activity above the mean is cross-hatched and is proposed to be due to parasympathetic activation. Root vS4.

B. Detrusor pressure (pressure difference) changes taken from 'C'. Note that changes in the detrusor pressure show almost exactly the same time course as do the activated changes of the secondary muscle spindle afferent fibre SP2(1) of 'A'. Corresponding peaks are correlated by arrows.

C. Abdominal pressure (measured as rectal pressure), intravesical pressure (urinary bladder pressure) and detrusor pressure (pressure difference) during retrograde filling before the surgery. One transient detrusor pressure increase, marked 'B', is used, after enlargement in 'B', to compare with the spindle afferent activity.

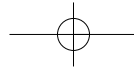
patient with a lesion sub C3 (artificial ventilation), with no tubus placed in the trachea and extremely light Propofol-anesthesia, there seemed to be a slight

detrusor pressure increase upon retrograde bladder filling. On the other hand, strong (painful) bladder catheter pulling activated the detrusor to contract in paraplegics with no anesthesia, most likely activated the parasympathetic nervous system in the brain-dead human HT6 (no anesthesia, possibly partial spinal shock), and seemed to activate the parasympathetic division during very light anesthesia. It is concluded therefore that painful stimulation of the bladder under light anesthesia activated the detrusor.

In Fig. 6, the increase in detrusor pressure upon retrograde bladder filling before surgery is compared with the activity increase of the secondary muscle spindle afferent fibre SP2(1) following 4 times bladder catheter pulling. Fig. 6A shows the undulating activity increase of the SP2(1) fibre from Fig. 5A. In Fig. 6C the cystogram is shown. Upon bladder filling spontaneous micturition occurred several times. If parasympathetic fibres really activated muscle spindles, then the activity increase of the secondary muscle spindle afferent fibres following bladder catheter pulling may have a similar time course as does the bladder pressure increase due to detrusor activation following retrograde bladder filling. To check this similarity of time course, one undulating increase of detrusor pressure (Fig. 6C) has been brought to the same time scale as the measured changes in muscle spindle afferent activity (Fig. 6A) and transferred into Fig. 6B for a direct comparison with Fig. 6A. By comparing Fig. 6A with Fig. 6B, it can be seen that the occurrence of activity peaks of secondary spindle afferents is very similar in its time course to that of the peaks of the detrusor pressure. From the similarity of changes of spindle afferent activity and detrusor pressure (4 peaks) it can be concluded that some muscle spindles in the domain of the sacral parasympathetic nucleus are partly controlled by the parasympathetic division and that the muscle spindle and the detrusor activation have similar time courses.

The other retrograde bladder filling induced undulating transient increases in pressure shown in Fig. 6C had a similar time course.

Another correlation could be found between detrusor pressure and muscle spindle activation. The bladder pressure in paraplegic 5 (Fig. 2) increased steadily with no or only little undulations, probably because the functions of the parasympathetic ner-



vous system were still relatively preserved. The activity increase of a secondary muscle spindle afferent fibre in paraplegic 5 was also sustained and only little undulating, as can be seen from Fig. 10.

Thus there is indication for some muscle spindles being partly driven by the parasympathetic division. The drive can be by parasympathetic fusimotor activity or more indirectly by somatic fusimotors. Since in HT6, the somatic fusimotors did not change their activity levels strongly with the activation of preganglionic parasympathetic fibres (Fig. 7 of (56)) and the activity increase of the secondary muscle spindle afferent fibre SP2(2) (Fig. 8) followed the transient increase of parasympathetic activity, it is likely that some muscle spindles are directly controlled by parasympathetic fusimotors. The direct control of some muscle spindles by parasympathetic fusimotors is supported by the slow activity decrease following very high activation (Fig. 12B,D) and the similarity

with the time course of the detrusor pressure decrease following electrical stimulation of the preganglionic parasympathetic fibres during the surgery. The slow spindle afferent activity decrease would be difficult to explain by somatic fusimotor activation only.

Detrusor-sphincteric synergy of the bladder in the brain-dead human HT6, and dyssynergia in paraplegic 9

The measurement of parasympathetic activation of the detrusor by activity changes of secondary muscle spindle afferent fibres (the spindle is innervated by parasympathetic fusimotors) allows an analysis of detrusor-sphincteric dyssynergia using the natural simultaneous impulse patterns of secondary muscle spindle afferents and sphincteric α_2 -motoneurons (and γ -motoneurons).

Dyssynergia of the urinary bladder in Para 9 and Synergia in brain death (HT6)

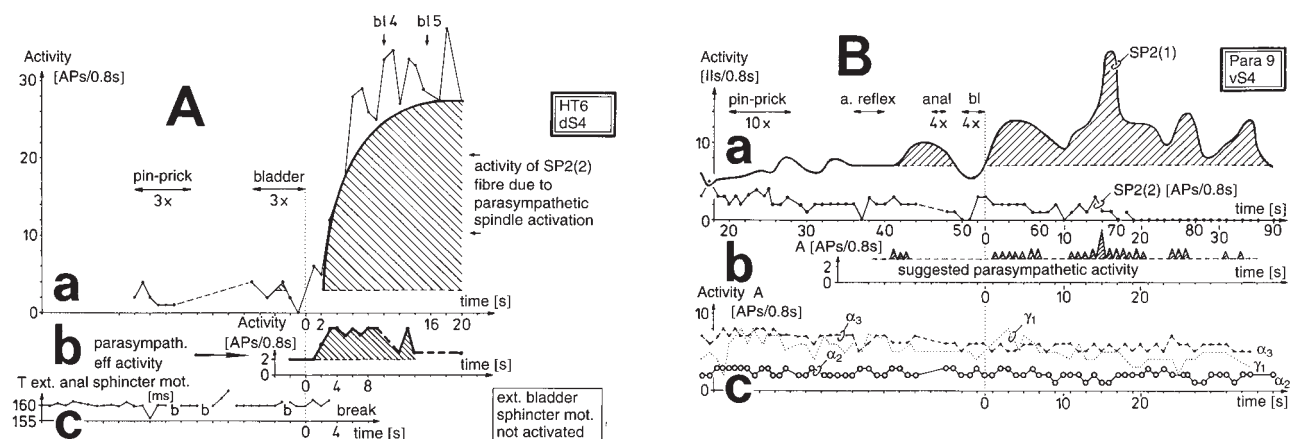


Fig. 7. – Direct comparison of secondary muscle spindle afferent and motoneuron activities between brain-dead human HT6 with no dyssynergia of the bladder (A) and paraplegic 9 with dyssynergia of the bladder (B).

A. Simultaneous measurements of activities of secondary muscle spindle afferents (a), parasympathetic preganglionic motoneurons (b) and oscillatory firing (high activity mode) of a sphincteric motoneuron innervating the striated anal sphincter (c). Note that with the transient activity increase of the parasympathetic fibres (b) the secondary muscle spindle afferent fibre increased strongly its activity (a) for minutes, and the oscillatory firing sphincteric motoneuron discontinued its oscillation (c) to reduce strongly its activity. bladder 3x = 3 times bladder catheter pulling. T ext. anal sphincter mot. = oscillation period of the sphincteric α_2 -motoneuron innervating the anal sphincter. For further details, see (56).

B. Simultaneous measurements of activity of secondary muscle spindle afferent fibres SP2(1) and SP2(2) following anal (anal 4x) and bladder catheter pulling (bl 4x) (a), and the activity changes of an α_2 -motoneuron (FR) and α_3 -motoneuron (S) and a dynamic fusimotor fibre (γ_1) (c). Note that following bladder catheter pullings (and probably parasympathetic activity increase), the spindle afferent fibre SP2(1) (most likely contributing to continence) increased its activity in an undulating manner (a), whereas the SP2(2) fibre did not (probably not connected to continence) (a), and the α -motoneurons did not reduce their activity (c). The dynamic fusimotor γ_1 transiently increased its activity similarly as in HT6 measurements (see Fig. 7 of (56)). In similarity to 'Ab', the suggested parasympathetic activity increase is pictured (b). a.reflex = anal reflex stimulation. IIs = interspike intervals; IIs/0.8 s = (APS - 1)/0.8 s (the activity measures IIs/0.8 s and APs/0.8 s differ by '1').

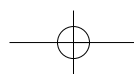


Fig. 7A shows that in the brain-dead human HT6, whose parasympathetic preganglionic neurons increased activity (Fig. 7A,b) upon bladder catheter pulling, the SP2(2) fibre activity increased strongly, whereas the α_2 -motoneuron innervating the external anal sphincter discontinued its oscillatory firing, which is a measure for a strong activity decrease. An α_2 -motoneuron, innervating the external (striated) bladder sphincter, was not activated. This means that with the activation of the detrusor the sphincteric motoneurons were relaxed by inhibition. Thus, the brain-dead human HT6 had a detrusor-sphincteric synergy of the bladder.

In paraplegic 9 who showed strong activity increase of the SP2(1) fibre, there was no sphincteric relaxation following bladder catheter pulling (Fig. 7B). The secondary muscle spindle afferent fibre SP2(1) increased its activity in an undulating manner (Fig. 7Ba). The parasympathetic fusimotors, driving the muscle spindle innervated by the SP2(1) fibre, probably were not continuously active as suggested by Fig. 7Bb, in contrast to the parasympathetic activity observed in HT6 (Fig. 7Ab). The other secondary muscle spindle afferent fibre in paraplegic 9 (SP2(2), Fig. 7Ba) slowly reduced its activity upon bladder catheter pulling. This spindle afferent fibre was not connected to the continence of the bladder. Probably, its spindle was not parasympathetically innervated and was sited in leg muscles or parts of the pelvic floor muscles not contributing to continence. The α_2 and α_3 -motoneurons (Fig. 7Bc) showed a high activation, which is expressed in their oscillatory firing (see later), and probably contributed to the continence of the bladder and the rectum. These, probably sphincteric, motoneurons did not reduce their activity following parasympathetic activation, as can be seen from the SP2(1) fibre activity (monitoring parasympathetic activity). These motoneurons were not inhibited and probably the external sphincters were not relaxed. The somatic fusimotor γ_1 (Fig. 7Bc) increased transiently and slightly its activity upon painful bladder catheter pulling, in similarity to a γ_1 fibre in HT6 (Fig. 7B of (56)). The measurements in paraplegic 9 indicate a loss of the inhibitory action of the detrusor onto the sphincteric motoneurons. However, there is no activity increase of the motoneurons with the increasing detrusor pressure, as suggested by Fig. 2 (Fig. 7Bc).

Natural impulse patterns of afferents and efferents of para 9 and HT6

To reveal possible reasons for the loss of inhibition, simultaneous afferent and efferent impulse patterns have been analyzed. In Fig. 8, the impulse patterns of HT6 and paraplegic 9 can be compared

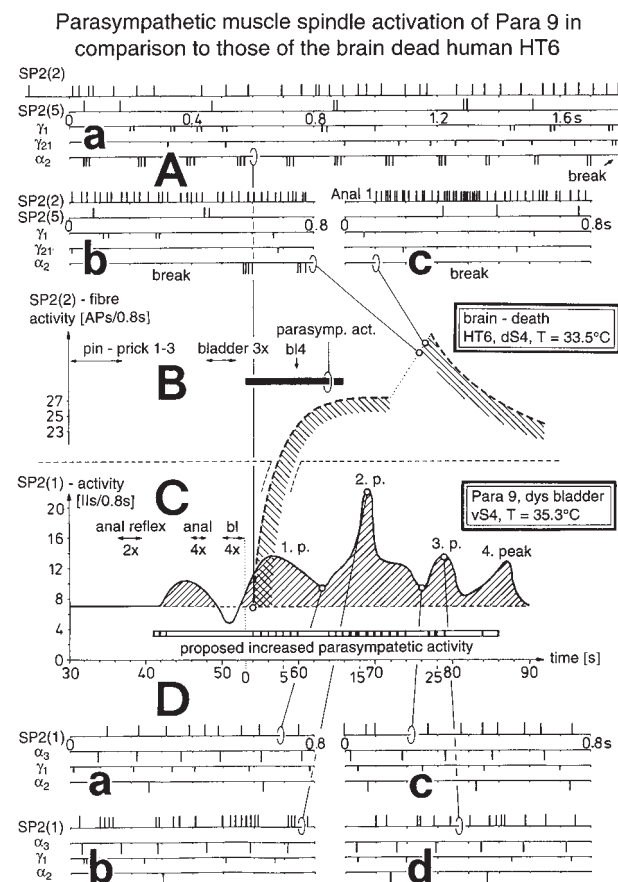


Fig. 8. – Comparison of muscle spindle afferent and efferent, and α -motoneuron activities between the brain-dead human HT6 (synergia of the bladder) (A,B) and paraplegic 9 with dyssynergia of the bladder (C,D). From same recording as in Fig. 7. Figs. 8B,C are put close together to improve direct comparison. A. Natural impulse patterns of the secondary muscle spindle afferent fibres SP2(2) and SP2(5), the fusimotors γ_1 (dynamic) and γ_{21} (static) and the sphincteric α_2 -motoneuron following bladder catheter pulling (bladder 3x). B. Activity increase of the SP2(2) fibre following bladder catheter pulling and parasympathetic activity (parasymp.act.) increase. C. Activity increase of the secondary spindle afferent fibre SP2(1) following anal (anal 4x) and bladder catheter (bl. 4x) pullings. Proposed parasympathetic activity increase indicated. D. Natural impulse patterns of the secondary muscle spindle afferent fibre SP2(1), the single α_2 and α_3 -motoneurons and the fusimotor γ_1 following anal and bladder catheter pullings.

directly. In HT6, the secondary muscle spindle afferent fibre SP2(2) showed an impulse pattern, with the interspike intervals (IIs) rather similar (Fig. 8Ab); irregularities in the pattern occurred only when the number of recruited encoding sites changed (Fig. 8Aa,c). In paraplegic 9, the activity of the SP2(1) fibre was lower (Fig. 8Da,c) and less regular (Fig. 8D,b,d). Probably this reduced activity in the SP2(1) fibre was due to a reduced parasympathetic activation, since an only little parasympathetically activated spindle afferent fibre can be expected to show more doublet firing, somehow similar to the SP2(5) fibre in HT6 (Fig. 8Aa). The impulse patterns of the parasympathetically driven spindle afferent fibres will be considered below. The other main difference in the impulse patterns between the brain-dead HT6 and the paraplegic was the different oscillatory firing of the α_2 -motoneurons. In HT6, the α_2 -motoneuron fired regularly with impulse trains consisting of 2 or 3 APs every 160 ms (6.25 Hz), whereas in paraplegic 9 the α -motoneurons fired irregularly in an oscillatory manner with impulse trains consisting of 1 AP every 130 ms (α_3 , 7.7 Hz) or 320 ms (α_2 , 3 Hz). The neuronal networks, driving the sphincters, had changed their properties completely. This indicates that the neuronal networks in paraplegics are damaged or malfunctioning. The function of the spinal oscillators in paraplegics will be analyzed in more detail in a following paper (84), where the parasympathetic action onto the somatic division will be studied in detail. Here, the impulse patterns of the secondary spindle afferent fibres will be considered further, to find out what has changed in the parasympathetic nervous system of the micturition center.

So far, there is indication for pathologic changes occurring in the functioning of the parasympathetic and the somatic divisions and in the interaction between both systems following spinal cord injury.

Differences in the impulse patterns of secondary muscle spindle afferent fibres between paraplegics and the brain-dead human HT6

Fig. 9 shows the impulse patterns of parasympathetically driven secondary muscle spindle afferents in paraplegic 9 and the brain-dead human HT6. In the brain dead individual (Fig. 9B), the activity was

low before strong bladder catheter pulling and increased strongly continuously and regularly following stimulation. In paraplegic 9, the activity level was higher before bladder catheter pulling and increased slower, in an undulating and irregular manner following catheter pulling. The burst-like firing seen in paraplegic 9 did not occur in HT6. The doublet firing was less regular in para 9 (Fig. 5). Specific properties in the drive of the spindle seem to be lost in the paraplegic. Even though a burst-like firing also occurred once in HT6 (Fig. 9Ba), the afferent fibre in HT6 could generate a sustained high regular activity level, whereas the fibre in paraplegic 9 could not.

The increase in the detrusor pressure in paraplegic 9 during retrograde bladder filling was very pathologic, since there was nearly no storage phase and the pressure increased transiently and in an undulating way (Fig. 6C). In paraplegic 5, the detrusor pressure curve was more physiologic since there was a storage phase of 350 ml and a sustained and only little undulating pressure increase upon retrograde bladder filling (Fig. 2). It is therefore of interest to see whether the impulse pattern of a secondary muscle spindle afferent fibre in paraplegic 5, driven by the parasympathetic division, was also closer to the impulse pattern obtained in HT6. Fig. 10B,C shows the interspike interval (II) distribution histograms and impulse patterns in dependence on time for paraplegic 5. Indeed, the afferent fibre patterns in paraplegic 5 were quite similar to those observed in HT6 (Fig. 9B). The impulse activity of the spindle afferent fibre was high, sustained, but still less regular than that in HT6. For low activity levels, impulse patterns similar to burst firing occurred (Fig. 10C). The doublet firing was less regular (Fig. 10C (32 s)) than in HT6 (Fig. 10A). Especially very short IIs occurred ($II < 1$ ms), which were not observed in HT6.

The bladder function in paraplegic 11 was also very pathologic. The storage volume before the surgery was 80 ml. The detrusor activity level was plateau-like and undulating with a frequency of 0.08 Hz. After deafferentation the storage volume increased to over 500 ml. A secondary muscle spindle afferent fibre fired with bursts of up to 6 APs with increasing II (Fig. 11d,e). The shortest safely observed II had a duration of 0.19 ms (Fig. 11c), which gives a transmission frequency of 5260 Hz.

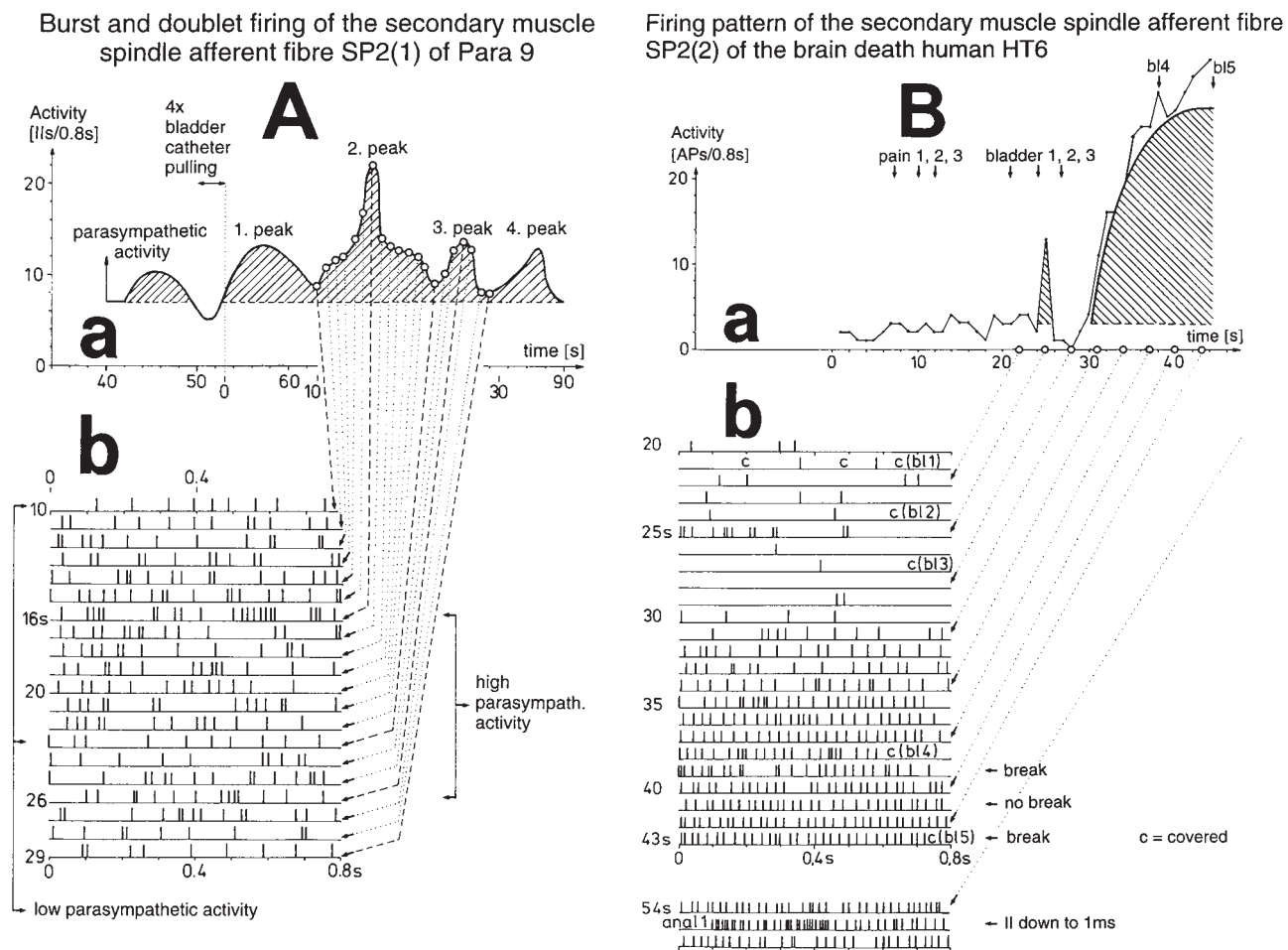
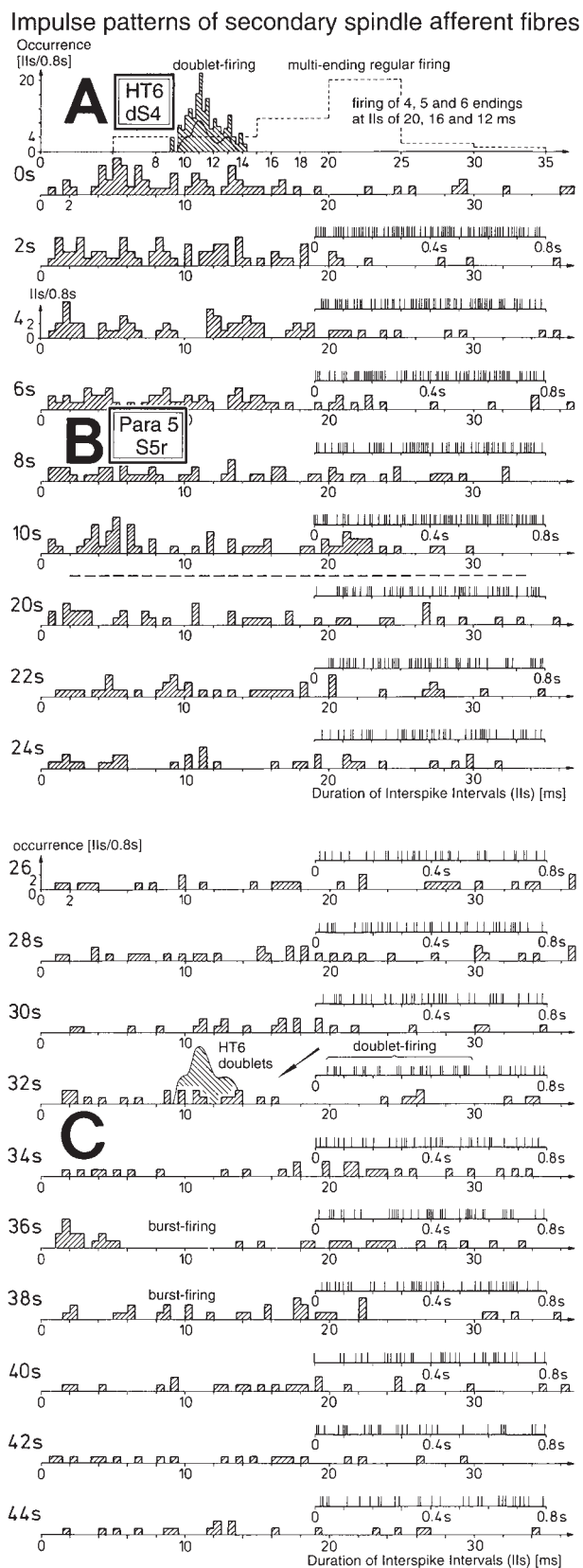


Fig. 9. – Comparison of the natural impulse patterns of single afferent fibres between paraplegic 9 with dyssynergia of the bladder (A) and the brain-dead human HT6 (B) with synergia of the bladder. Activity increase of the spindle afferent fibres following bladder catheter pullings (a) and the natural impulse patterns at different times following catheter pullings (b). A. Note that at activity peaks (a) there was burst firing in paraplegic 9, (marked by the arrows, 16 s, 26 s), and at low activity (a) there was no burst firing (10 s, 23 s). B. Note that even though burst firing appeared also in the brain-dead (25 s), the activity increase sustained with similar interspike intervals (IIs). break = break of oscillation of sphincteric motoneuron. c = covered = skin afferent action potentials covered SP2 fibre impulses due to bladder catheter pullings (bl 1 - bl 5).

The afferent activity in paraplegic 11 was very high (Fig. 11d,e) as was the efferent activity (Fig. 11f), as if the nervous system was strongly overactivated and therefore malfunctioning. In this root S5, burst firing was observed in more than 10 secondary spindle afferent fibres, consisting of up to 6 APs with increasing II. The shortest II observed had duration of 0.18 ms, and the II largest in a burst had duration of 18.5 ms. Since different spindle afferents showed different bursts, there seemed to be a different parasympathetic drive for each spindle. The para-

sympathetic fusimotor drive may be as complex as the somatic one.

From the S5 root was frequently recorded, because the root is thin (83) and normally not saved (deafferentation), when implanting an anterior root stimulator for bladder control. The S5 root was saved when, due to a variation, the root carried many pre-ganglionic parasympathetic motoneuron fibres as verified by the bladder pressure increase upon electrical stimulation of the S5 root. In contradiction to anatomy books, feet muscles are frequently activated



when lower sacral nerve roots (including S4) are electrically stimulated. Nerve fibres innervating leg muscles may even lead sometimes through the S5 root.

In paraplegic 5, the bladder function was only slightly pathologic. It was therefore of interest to also consider the functional stage of the somatic division in this patient. Even though the oscillatory firing motoneurons showed quite a variation in their oscillation periods, the impulse train of each cycle was rather physiologic. The sphincteric α_2 -motoneuron innervating the external anal sphincter fired with 3 APs every 167 ms on average and with a first and a second II of 4.3 and 8.5 ms very similar to the values observed physiologically (HT6, (47)). The α_2 -motoneuron innervating the external bladder sphincter fired with impulse trains consisting of 1 to 2 APs (II = 7.4 ms) every 111 ms, also very similar to the firing pattern observed in HT6 (47). Thus, the somatic division in the paraplegic 5 was, similarly as the parasympathetic one, not too pathologic either. The main problem in paraplegic 5 was dyscoordination of the detrusor and the striated bladder sphincter.

The impulse patterns of γ -motoneurons and parasympathetic fibres could partly be identified in the S5 recording in paraplegic 5, but it was not possible to follow them up over longer time intervals. Besides the high parasympathetically activated SP2 fibre a further identified secondary muscle spindle afferent fibre (SP2') fired with doublets at a low activity level, indicating a low parasympathetic activation. Simultaneous firing of secondary muscle spindle afferent fibres with low and high parasympathetic activation was also found in the brain-dead human HT6. In Fig. 8Aa, fibre SP2(2) increased its activity strongly, whereas fibre SP2(5) fired with doublets at low activity levels.

It is satisfying that the results obtained with the single fibre AP recording method from impulse pat-

Fig. 10. – A. Histogram of doublet firing and multi-ending regular firing in the brain-dead individual HT6 (synergia of the bladder), same histograms as in Fig. 5C.

B,C (0 s–44 s). Interspike intervals and impulse patterns for a secondary muscle spindle afferent fibre of paraplegic 5 (with dyssynergia of the bladder) in dependence on time. The occurrence of doublet and burst firing indicated. Note that the impulse patterns are more regular than in paraplegic 9 (Fig. 9Ab) with stronger dyssynergia, but less regular than in the brain-dead individual (Fig. 9Bb) with no dyssynergia.

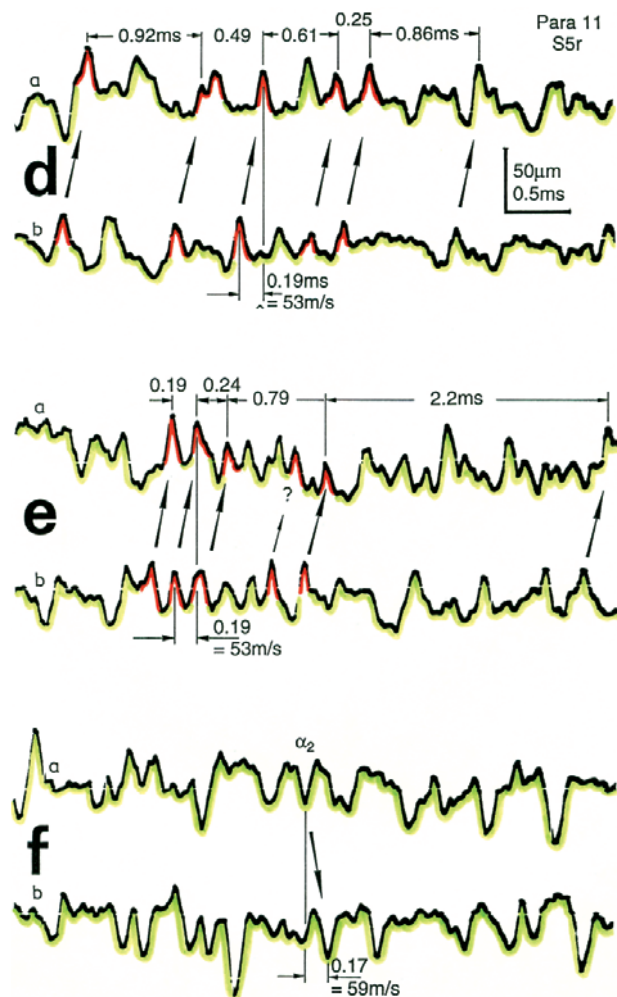


Fig. 11. – Afferent and efferent activity in an S5 root of paraplegic 11. d,e. Burst firing of secondary muscle spindle afferent fibres. Shortest II = 0.19 ms, which corresponds to a transmission frequency of 5260 Hz. f. Increased efferent activity. Note that if the afferent activity is high, the S5 root looks like a dorsal root (d,e), and if the efferent activity is high, the root looks like a ventral one. The AP (action potential) amplitude calibration 50 μ m designates 50 microvolt (50 μ V).

terns of afferent and efferent fibres support the results obtained urodynamically. The impulse patterns however will provide additional insight into the organization of the human nervous system under physiologic and pathophysiologic conditions.

Unaltered muscle spindles following spinal cord injury

It was shown in Figs.7,8,9 that the firing of the parasympathetically driven secondary muscle spin-

dle afferents of paraplegic 9 had changed in comparison to those of the brain-dead human HT6. The impulse pattern changes could have been due to a pathologic self-organization of the neuronal networks mainly of the spinal cord, due to changes in the muscle spindles or both. Changes in peripheral ganglia cannot completely be excluded. If one could show that the muscle spindles themselves remained unchanged, then most likely the pathologic function would be due to organization changes in the CNS.

Fig. 12B shows the activity decrease of a secondary spindle afferent fibre in paraplegic 5 following presumed parasympathetic activation. Original patterns are shown in Fig. 10B,C. Since most likely the spindle afferent fibre turned backward in the root (see below) its APs were uniquely marked with the time-locked efferent-like AP and the activity changes could therefore be measured safely.

The activity decrease of the secondary spindle afferent fibre (Fig. 12B) was assumed to be of the e-functional type. The time constant τ_{off} (Fig. 12D) was 25 s. Since there was a slight additional activation between 30 and 50 s, a successive calculation of the time constant was performed ($\tau_{\text{off}} = 36$ s) and a mean τ_{off} of 31 s was obtained (Fig. 12B,D).

The time constant for the activity decrease of the secondary muscle spindle afferent fibre in paraplegic 5 (31 s) is similar to the value obtained for the brain-dead human HT6 ($\tau_{\text{off}} = 40$ s, (56)). Following electrical stimulation of preganglionic parasympathetic fibres during the surgery, the detrusor pressure decreases slowly with an e-functional time constant of approx. 30 to 40 ms. It is therefore concluded that the passive properties of the muscle spindle with respect to the parasympathetic innervation had not changed. It is further concluded that the changes in the natural impulse patterns of the parasympathetically activated secondary muscle spindle afferent fibre were caused by changes in the networks of the parasympathetic nucleus in the sacral micturition center.

Turning of nerve fibres

Fig. 12A shows an afferent AP, which is followed by a time-locked efferent-like AP. The conduction times on trace 'a' and trace 'b' are plotted in Fig. 12C against each other, as indicated in 'A'. It can be seen

that the correlation points lie on a straight line and are grouped in two areas. It seems therefore that sometimes the fibre conducted with a slower velocity. Probably the efferent like AP is not a reflected AP, since otherwise the correlation points would be more scattered. Also, a reflected and antidromically conducted AP would cancel out a closely following orthodromically conducted AP. This was not the case. An SP2 fibre AP reaching the recording electrodes 0.5 ms later (Fig. 3b) would have a spatial delay of 25 mm ($v = s/t$; $s = vt = 50 \text{ mm/ms} \cdot 0.5 \text{ ms} = 25 \text{ mm}$). In a previous paper (83) the distance between the urinary bladder and the recording elec-

trodes in the spinal cord was calculated to exceed 300 mm. A reflected SP2 fibre would therefore cancel out the AP arriving 0.5 ms later. It is concluded that the secondary spindle afferent fibre performed a loop or branched in the root. A cross-talk of nerve fibres (ephaptic transmission) is unlikely because of the regularity of firing.

The branching of nerve fibres in roots or the performing of loops is probably seldom and unimportant. Here, such situations are of special interest since they mark uniquely the activity of single fibres. For nerve fibre branching and nerve fibre loops in nerve roots, see (12).

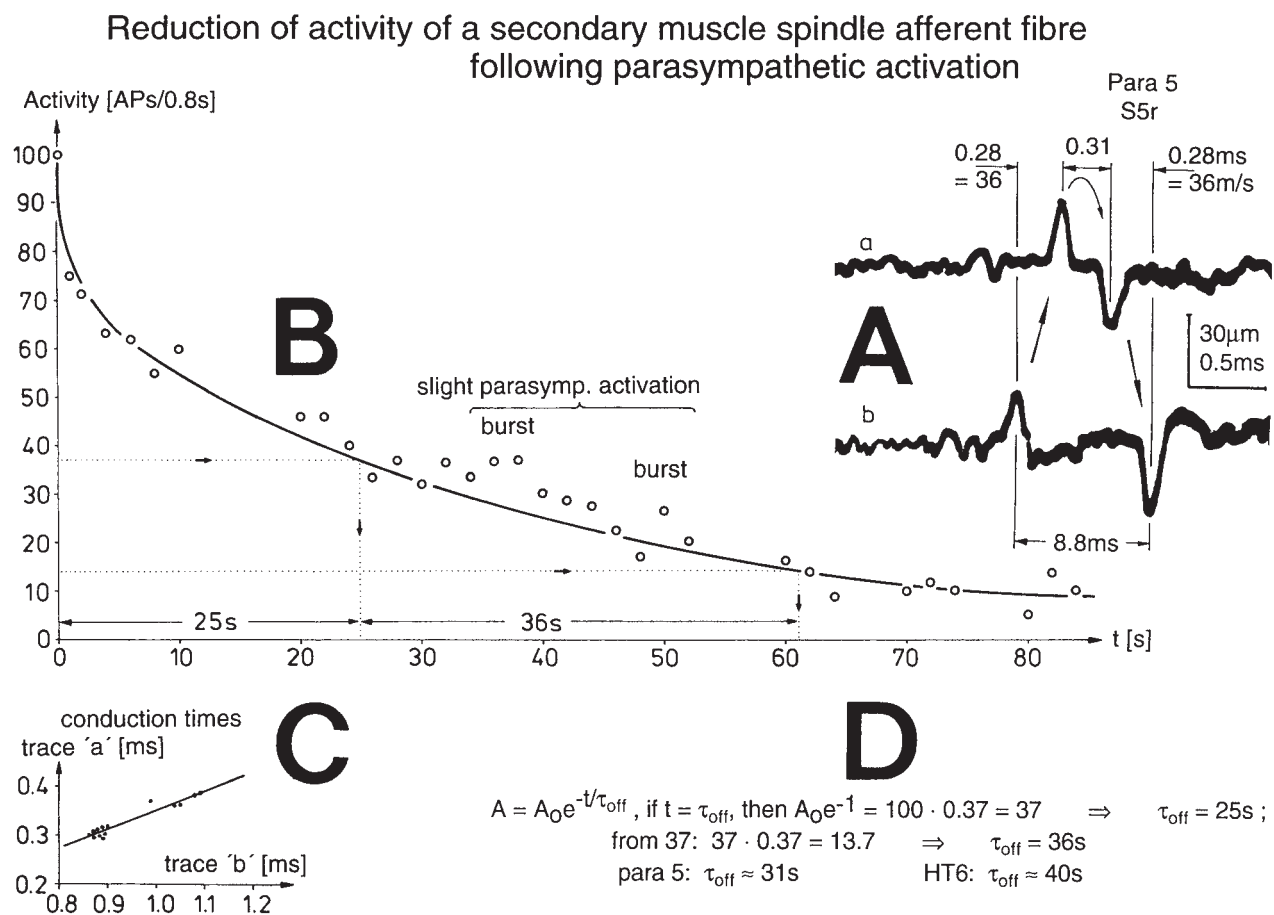
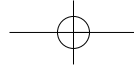


Fig. 12. – A. Recording from a secondary muscle spindle afferent fibre which is uniquely marked by its efferent-like AP of the turning fibre. B. Activity reduction of the spindle afferent fibre following parasympathetic activation; impulse patterns are partly shown in Fig. 10. e-functional decline is disturbed gently by further slight parasympathetic activation in the form of bursts. Time constants for e-functional decline τ_{off} are indicated.

C. Relation between conduction times on trace 'a' and trace 'b' as indicated in 'A'. D. Calculation of the time constants for the e-functional decline. The AP (action potential) amplitude calibration 30µm designates 30 microvolt (30µV).



Discussion

Membrane properties

Figs. 3,5,11 show interspike intervals of single secondary muscle spindle afferents down to 0.19 ms. The corresponding naturally evoked transmission frequencies give 5000 Hz and more. Expected were transmission frequencies of less than 1000 Hz (24); text books for medical students give values of transmission frequencies of between 500 and 1000 Hz (87). Absolute refractory periods in the range of 0.2 ms therefore indicate that the membrane properties of secondary muscle spindle afferent axons in humans differ from those of animals. If axons of interneurons in the central nervous system (CNS) also had 5 times higher transmission frequencies, then CNS functions could be speeded up in humans in comparison to those of laboratory animals.

It is difficult to understand, why in man group conduction velocities range 40% slower than in cat and dog (46,48,83). In comparing human and dog measurements, the higher conduction velocities in dogs seemed to be due to a larger nerve fibre diameter (48). Human nerve fibres seemed to slightly enhance the conduction velocity through the presence of a thicker myelin sheath, which would increase the internode length (44) and in that way increase the conduction velocity.

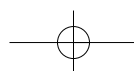
In the squid, conduction velocities are increased phylogenetically by an axon diameter enlarged up to 1 mm (24). Higher species developed the myelin sheath so that excitation jumps from one internode to the next one to increase conduction velocity. It is conceivable that in man the nervous system tried to improve processing and complexity by increasing transmission frequency and reducing nerve fibre diameter at the price of reduced conduction velocities. In modeling human CNS functions, one probably has to consider membrane properties typical of human membranes.

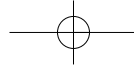
Transmission frequencies, refractory periods and times of inactivation of nerve cells are important for the function of the CNS. To compare the trophic influence data for frogs to those for humans, to look for similarities, when working on the trophic influence (40,60), the body temperature of living frogs was increased up to 37°C. The frogs (*Rana tempo-*

rarica) died at temperatures of between 29 and 30°C. Two kinds of frogs from Brazil also died at that temperature. Before the frogs died, they developed very strange behavior. Sexual reflexes or movements occurred. They resembled spasms in paraplegics. The CNS of the frogs probably developed pathologic functions due to the too high temperature. Probably, a too high impulse traffic occurred in the CNS. If one believes that the neuronal network of the CNS is not purely constructed of dedicated lines of excitation but also of synfire chains which cross each other (Fig. 25 of (1)), then refractory periods of nerve cells may become of high importance. A reduction of refractory periods may allow a speeding up of CNS functions, since the crossing of excitation via crossing of synfire chains is possible at higher impulse traffic or gives more safety for physiologic functioning. One reason for the pathologic function of the disconnected spinal cord in paraplegics may be overexcitation of the CNS. The exceedingly high activity in the disconnected spinal cord may contribute to spasticity and urinary bladder dysfunction. This problem will be picked up again in a following paper (84), when discussing dysfunctions of spinal oscillators (53).

Muscle spindle afferents activated by the parasympathetic division

In a previous paper it has been reported that some muscle spindles in the lower sacral range were most likely activated by the parasympathetic division (56). The physiologic parasympathetically induced activity patterns of the secondary muscle spindle afferents seemed to be the multi-ending regular firing for high activation and the doublet firing for low parasympathetic activation. Since a secondary spindle afferent fibre increased its activity following a transient activity increase of preganglionic parasympathetic motoneurons, even though the somatic fusimotors did not change their levels strongly, it was concluded that most likely the parasympathetic division directly activates the spindles; this means that muscle spindles are innervated by parasympathetic fusimotors (56). The direct control of some muscle spindles by parasympathetic fusimotors is supported by the slow activity decrease following very high activation (Fig. 12B,D) and the



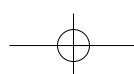


similarity with the time course of the detrusor pressure following stimulation of the preganglionic parasympathetic fibres during surgery. Such a slow spindle afferent activity decrease would be difficult to explain by somatic fusimotor activation only. More direct comparisons between activity levels of parasympathetic fibres and those of secondary muscle spindle afferents are needed. The recordings for such comparisons are difficult to obtain because the thin preganglionic parasympathetic motoneuron fibres generate only APs of small amplitude (Fig. 3 of (83)). Further support for parasympathetic fusimotor drive comes from Fig. 12. No slow e-functional decrease in the secondary muscle spindle afferent activity from very high levels is found following somatic fusimotor activation. Sometimes intrafusal muscle fibres are compared with the slow muscle fibres of the frog. It has been shown that slow muscle fibres are under the trophic control of the nerve fibres they are innervated by, even before synapses start to function electrically (34,42). The controlled functions include excitability of membranes and excitation-contraction coupling. It has further been shown that partially denervated slow muscle fibres of the frog partly change their functional properties in the denervated muscle fibre but remain unchanged in the still innervated area (39,41). Protein synthesis in the several nuclei of a muscle fibre is probably stimulated differently for corresponding membrane changes of the muscle fibre. It is therefore conceivable that parts of intrafusal muscle fibres are innervated by parasympathetic fusimotors. Morphologic support is needed. So far few data are available concerning the morphology (28) and the electrophysiology (20,21) of the human muscle spindle outside the parasympathetic domain. In animals some muscle spindles in the domain of the sympathetic division are innervated by sympathetic fibres (2,3,10,37). It was further shown that parasympathetically driven muscle spindles are found in the domain of sacral parasympathetic division but not outside of it (Figs. 3,4 of (57)). The high activity of secondary muscle spindle afferents (primaries are seldom found in the lower sacral range) can partly be split into the impulse patterns of the up to 6 encoding sites of parent fibres (54,56,57) with impulse patterns of the single endings similar to those obtained from spindle afferent fibres activated by somatic fusimotors only (10,72).

It remains unclear whether the supposed parasympathetic fusimotors have the same caliber as the preganglionic parasympathetic motoneurons synapsing on ganglion cells to innervate the detrusor. The classification scheme of the human peripheral nervous system (46,83) needs further improvement. A previous paper (Figs. 1,8 of (56)) suggested a possible existence of several kinds of parasympathetic fibres. In paraplegic 11 (Fig. 11), there were more than 10 secondary spindle afferent fibres firing with bursts of different interspike intervals, indicating that the spindles may have obtained different fusimotor drives. In recordings of para 5 it could be seen that at the same time some muscle spindles were highly (multi-ending regular firing or burst firing) while others only little parasympathetically activated (doublet firing). It seems therefore possible that parasympathetic efferent fibres also split up into different groups with different properties. The similarity of the time course between activity level changes of parasympathetically driven secondary muscle spindle afferents and detrusor pressure changes (Fig. 6) point more towards simpler common parasympathetic activation, but since the time course is slow and includes smooth muscle fibre activation, changes are covered.

Similar time courses of detrusor pressure and secondary spindle afferent activity changes

The similarity between detrusor pressure changes before the surgery, induced by retrograde bladder filling, and spindle afferent activity changes under light anesthesia, following painful bladder catheter pulling, in the 3 paraplegics studied are of interest for several reasons. The clinically most important question is: why does the detrusor get not activated during anesthesia by retrograde bladder filling, but is activated by painful bladder catheter pulling. Somnolent patients who do not respond to speech and touch can be waken up with the application of somatic pain. In similarity to somatic pain application it is conceivable that pain application in the parasympathetic division is a stronger stimulus for the activation of the detrusor than the firing of stretch (S1) and tension receptor afferents (ST). If this is so, then it could further be that parasympathetic afferents, conducting pain, are activated by



inflammation as probably do stretch and tension receptor afferents. A hyperreflexia of the detrusor could then partly be due to sustained activation of parasympathetic pain afferents. A nearly complete deafferentation of the bladder stops the hyperreflexia of the detrusor, and large storage volumes of the bladder can be obtained after some time again. The deafferentation surgery not only cuts the thick afferents of stretch and tension receptors, but also the thin fibre populations, including parasympathetic pain afferents. Also, the rather thin afferent fibres of the flow receptors are cut (46). If these afferent fibres were stimulated by inflammation, the sacral micturition center would all the time get the message that urine is passing through the trigonum vesicae and the urethra, and bladder reflexes would probably be activated to sustain voiding (possible descending inhibitory control of the afferent input is destroyed by the spinal cord injury). Tetraplegics with a partial spinal cord injury report that during bladder infection there was a complete dysfunction of the bladder. However, as soon as the infection wore off, the bladder started to work acceptably again. Therefore, patients with an inflammation must be free of infection for some time before prognosis concerning their bladder function can give meaningful answers.

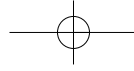
Nearly all humans get bladder infections following spinal cord injury. The problem is how to improve bladder function to get rid of reoccurring infections. It was the benefit of Sir Guttman (23) to introduce the 'intermittent catheterization' so that the patients could avoid infections caused by the bladder catheter. But patients with severe cervical spinal cord injury have no hand functions left to perform this intermittent catheterization by themselves. It is the benefit of this current human research that it is possible to cure urinary bladder function in severe cervical spinal cord injury (86), so that all urinary bladder complications including reoccurring infections, hyperreflexia and dyssynergia (with development of compliance changes, high bladder pressure and urinary tract damage) are not occurring any more or cured if proper coordination dynamics therapy is started one or two weeks after the injury and is administered for at least 3 years.

The similar time courses of detrusor pressure and secondary muscle spindle afferent activity provides information about the time course of the bladder

pressure from the activation of spindle afferent fibres and allows analyzing dysfunctions, even though it is not well understood what underlies these similar time courses. Probably, parasympathetic motoneurons activate the detrusor and intrafusal muscle fibres with approximately the same time course. Interesting is further that this parasympathetic motoneuron activation is rather stereotypic and does not change very much under light anesthesia.

Replacement of physiologic multi-ending regular firing by pathophysiologic burst firing

As observed in the brain-dead individual, the low activity level doublet firing and the high activity level multi-ending regular firing (Fig. 9B) probably represents physiologic parasympathetic activation of secondary muscle spindle afferent fibres with coordinated firing of several endings of the parent spindle afferent fibre. In paraplegics with detrusor-sphincteric dyssynergia and spasticity, these firing patterns were changed and mixed. In paraplegic 5 with slight bladder dysfunction the multi-ending regular firing was somehow preserved (Fig. 10B,C). In paraplegics 9 and 11 with strong bladder dysfunctions the multi-ending regular firing was replaced by a burst-like firing (Fig. 9A, Fig. 3C, Fig. 11d,e). If one assumes that on average the spindles are activated in parallel to the activity of the preganglionic parasympathetic neurons, as suggested in Figs. 7Bb,8C, then the parasympathetic nucleus in the sacral micturition center seems to be unable to develop a sustained activation anymore. It is not known whether parasympathetic motoneurons also can fire in an oscillatory manner for high activation levels (see (84)). If it were so, then these oscillators could only fire in a transient oscillatory mode. In the brain-dead individual a sphincteric α_2 -motoneuron (FR) fired transiently oscillatory upon retrograde bladder filling, because the activity level from stretch and tension receptor afferents was low (47). The motoneuron fired continuously oscillatory for high afferent input but was slightly inhibited for very high afferent input (Fig. 9 of (55)). In the paraplegics the stretch and tension receptors were highly activated or partly overactivated (83), but the preganglionic parasympathetic neurons could not fire continuously oscillatory. It is therefore conceivable



that there was a dysfunction in the neuronal network activating the parasympathetic motoneurons, independent of whether the neuronal networks fired oscillatory or not. An overactivation of the neuronal network (see previous paragraph) may have contributed to the dysfunction.

The recorded bursts (Figs. 3c,11d,e) with the extremely short interspike intervals (shorter than 0.2 ms) suggest that parasympathetic neuronal networks tried strongly to generate a high activity level but they failed to sustain the activity, so they tried again and again. One could even imagine that the loss of inhibition onto the somatic sphincteric motoneurons exerted by the parasympathetic division (see below) is due to the loss of sustained activation. In paraplegic 5 (slight bladder dysfunction) however the developed detrusor pressure was sustained (Fig. 2) and also the impulse activity level of a secondary spindle afferent fibre was rather sustained (Fig. 10B(2 s)), but still the pelvic floor was activated rather than inhibited with the increasing detrusor pressure (Fig. 2). Thus, there may be several reasons for the dysfunction of the urinary bladder in paraplegics. Probably, some of them are key changes in or damages to the neuronal network below the spinal cord injury level which cannot be compensated for by the network itself. Only supraspinal control could substitute for the necessary control, which can be established (86). In the following paper (84) failures of the neuronal networks of the sacral micturition center will be analyzed by making use of the spinal oscillators.

Simultaneous action of the somatic and parasympathetic divisions

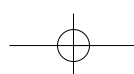
As outlined in the Introduction, physiologically there is hardly any somatic response to natural stimulation which is not accompanied by an autonomic reaction (19). In the cat spinal cord there is anatomical evidence for direct brain stem projections to the somatic motoneuronal cell groups and autonomic preganglionic cell groups (25). In paraplegics and tetraplegics (lesion sub C5/6 or more rostral) often somatic functions are destroyed because of the spinal cord injury, but autonomic responses are preserved or even enhanced. Such autonomic responses are often helpful for the patients to monitor functions

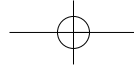
of the body, but they also can be unpleasant. A tetraplegic patient had been reporting all day long sweating in one half of the face for years. When a stricture of the urethra was revised, the sweating stopped. Sympathetic responses are common. The sympathetic chain is often undamaged following spinal cord injury. Reflex voiding is often accompanied by sweating or dangerous blood pressure increases. Bladder distension by retrograde filling can activate somatic spasticity (Fig. 2). Especially when the somatic and the autonomic nervous system have receptors in common, the stimulation of those receptors will simultaneously result in strong somatic and autonomic responses.

Parasympathetic activation of different strength can be seen in Fig. 5. In Fig. 5A the doublet activity levels of a secondary spindle afferent fibre are drawn, and in Fig. 5B the durations of the doublet interspike intervals following different natural stimulations are plotted. It has been mentioned that doublet firing is a measure for low level parasympathetic activation. As can be seen from Fig. 5A,B, only few doublets occurred upon touch and pin-prick stimulation. There was only little activation of the parasympathetic division. Upon anal reflex stimulation the parasympathetic response increased. Anal and bladder catheter pulling strongly activated the parasympathetic division as measured by the activity levels of doublet and burst firing. This was to be expected since catheter pulling activates continence functions.

Somatic and parasympathetic functions can be activated by common receptors. The anal canal is innervated by skin and mucosa afferents (52). Especially the T4 (possibly similar to SAII receptors in animals) skin afferent fibres are of interest, since their receptors are very sensitive to skin displacement. Probably, the T4 mechanoreceptors are strongly activated when a finger is moved along the skin with very light pressure ('streicheln'). They will contribute to the discrimination between wind, fluid and solid content, when material is passing through the anal canal. The skin afferents T1 to T4 will activate somatic (external sphincter contraction) and parasympathetic functions (sphincter inhibition, see following paper (84)).

Somatic and parasympathetic functions can be activated simultaneously by simultaneous stimulation of specific parasympathetic receptors and





unspecific receptors. With the pulling of the bladder catheter, stretch (S1) and tension receptor afferents (ST) were activated besides flow (S2), mucosal (M) and other receptor afferents including pain afferents. Even though stretch and tension receptors themselves probably activate parasympathetic responses in a rather specific manner, natural stimulation such as pulling of the bladder catheter or even distension of the bladder will simultaneously activate less specific receptors or even receptors which stimulate somatic functions. If the bladder catheter is accidentally pulled strongly in patients with remained sensibility in the bladder, the patients report pain instead of a wish to micturate. Patients with lost sensibility of only the bladder may still feel, to some extent, a filled bladder, because the distended bladder displaces adjacent structures or pushes against them. It has been reported that Pacinian corpuscles (PC = T1) can be activated over distances of up to 100 mm (52). The anchorage of the mechanoreceptors in the skin or other tissues is one reason for stimulation over long distances (26,27).

If in humans with spinal injuries the specific receptors (S1,ST) monitoring bladder storage volume (increase) are disconnected from supraspinal centers and if there are still connections preserved from unspecific mechanoreceptors, the training of these unspecific receptors may be of benefit for bladder fullness control, since normally the afferent input from the receptors is not being used efficiently. It has been reported for the skin that the two-point discrimination can be increased, since in the rather untrained situation there are 7 to 8 receptor innervations in between the 2 points of the two-point discrimination (52).

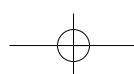
Possibly, also the afferent fibres innervating the adjacent structures of the urinary bladder may converge onto the same nerve cells as do bladder afferents. Convergence of visceral and cutaneous (Head's zone) afferent pathways has been reported in animals, including primates (17,62).

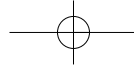
In a following article it will be shown that the urinary bladder function can be cured by a functional reorganization and limited regeneration in severe cervical spinal cord injury (86). A key movement for bladder repair is the jumping on springboard when no body-weight support is provided! Upon jumping rhythmically on springboard, the intestine, resting on the pelvic floor, will induce

rhythmic stretch and tension increases in the pelvic floor, including the external anal and bladder sphincters. Also the detrusor and the urethra will be stretched and pressed rhythmically. Many of the receptors of the urogenital domain, including stretch (S1), tension (ST), flow (S2), mucosal receptors (M), and mechanoreceptors T1 through T4, will be activated to give rise to an intermingled activation of the somatic and parasympathetic nervous systems. But especially the muscle spindles, involved in continence functions, innervated simultaneously by somatic and parasympathetic fusimotors with their spindle afferents projecting into somatic and parasympathetic networks, will give rise that the somatic and parasympathic divisions dovetail with one another. The doublet firing of the spindle afferents may even have a messenger function for communication between the systems. With the learning-based movement therapy 'coordination dynamics therapy', especially the jumping on springboard, a learning transfer (85) from movements to urinary bladder function for repair is therefore conceivable. But since there are several reasons for the dysfunction of the urinary bladder in patients with severe spinal cord injury with key changes in or damages to the neuronal network below the spinal cord injury level which cannot be compensated for by the network itself, only supraspinal control can substitute for full necessary control and learning. But it is not only the functional and structural repair which is needed. Within the system theory of pattern formation for repair (78,81), for describing integrative CNS functions, there are attractor states for the synergia pattern (for micturition) and the dyssynergia pattern (for stopping micturition) with different stabilities, which can be changed by learning and intention. Therefore some supraspinal control is needed for the repair of the networks and for choosing between different network patterns (see below).

Detrusor-sphincteric coordination

It is generally assumed that it is the level of the pons and the adjacent medulla at which coordination and integration of the bladder and the external sphincter activity occurs in the adult. Lesions above the brain stem lead to coordinated incontinence, and lesions below the brain stem centers but above the





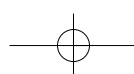
lumbosacral spinal cord lead, after a period of bladder paralysis associated with spinal shock, to involuntary reflex voiding that is not coordinated with sphincter relaxation (detrusor-sphincteric dyssynergia) (22,69). The measurements in the 3 paraplegics studied with clinically complete lesions below the brain stem and above the lumbosacral spinal cord and with detrusor-sphincteric dyssynergia support this view. Upon the activation of the parasympathetic division (Fig. 7B) the detrusor pressure increased (Fig. 6), but sphincteric α -motoneurons were not inhibited. In discordance with present view is that the sphincteric motoneurons in the brain-dead human were inhibited upon the activation of the parasympathetic division (Fig. 7A). One can escape the conclusion that in the brain-dead individual there was coordinated action between the detrusor and the sphincter, in arguing that the breathing center and other parts of the brain stem were destroyed but the pontine micturition center was still working. Such a situation may in principle be possible, since brain-death can be manifested in different ways. However, it is more likely that the whole brain stem was destroyed.

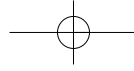
These measurements then seem to indicate that the detrusor-sphincteric coordination is not located in the pontine micturition center and that detrusor-sphincteric dysynergia develops during the 3 to 4 weeks lasting spinal shock phase when the micturition reflex via supra-spinal centers is replaced by a reflex via the sacral micturition center, in some similarity to that in infants. There is little doubt that important changes occur in the spinal shock phase. Nevertheless, putting the problem behind the term of the not yet understood spinal shock would not promote the solution to this problem. There seem to be important rearrangements during the spinal shock, so that a training of the sublesional CNS in paraplegics already has to start during the spinal shock phase. Of high importance for the understanding of micturition following spinal cord injury would be to obtain recordings, at least urodynamic, from paraplegics below the age of 1 year, to see whether micturition in infants is changed following spinal cord injury. Infants possess prominent micturition responses that can be initiated by light tactile stimulation of the perineum, the lower back, or by cutaneous contact with water (6,66).

Micturition in neonatal mammals of many species (rat, cat, guinea pig) (4,5,14,29,38) is regu-

lated by the mother. She initiates excretion by licking the perineum, and then she consumes the excreted waste, which conserves her bodily fluids to meet the demands of lactation (18) and prevents the odors of the wastes from attracting predators to the nest. Thus, micturition in the neonate is mediated by a spinal somatovesical reflex that is initiated by exteroceptive stimulation. In kittens, the somatovesical reflex pathway disappears about the time of weaning and is replaced by a vesicovesical reflex pathway that produces micturition via a supraspinal reflex pathway that is activated by interoceptive stimulation, i.e. bladder distension and, in addition, may be under voluntary control. Stimulation of the perigenital region in adult cats actually inhibits the supraspinal vesicovesical micturition reflex. Presumably, this inhibition serves to suppress micturition during copulation. Following spinalization, in older kittens, the excitatory somatovesical reflex consistently returns in less than a day, while in adult cats, the reflex returns more slowly and with greater variability, i.e. 2 days to 2 weeks (66,68).

Since micturition is a phylogenetically old function, coordination of the detrusor and the sphincter may well get support from several levels. There may already be some detrusor-sphincteric coordination in the sacral micturition center. The malfunctioning of different components in the reflex arc may result in the overriding of the weak detrusor-sphincteric inhibition. An already slight inflammation could be one cause. In normal humans with hemorrhoids the external anal sphincter may be sustained contracted following slight inflammation. Upon suppressing the inflammation (by eating garlic with some antiinfectious action), the external anal sphincter relaxes. With the inflammation intensifying, the external sphincter develops sustained contraction again, and it is nearly impossible for a normal human to voluntarily inhibit this contracture. It will be shown in the following paper what a dramatic activity increase does occur in the motoneurons innervating the external bladder sphincter upon pathologically high activity of stretch (S1) and tension receptor afferents (ST) from the bladder wall (84). As long as inflammation and infection of the lower urinary tract are not fully relieved, no information can be obtained about the possible functions of the sacral micturition center following spinal cord injury.





It has been suggested that bladder outlet obstruction in rats is accompanied by some degree of neural plasticity resulting in a more prominent spinal reflex that could contribute to the development of the unstable bladder following obstructions in humans and unanesthetized animals (71).

In a following article on the cure of the human urinary bladder function (86) there is support for the view that the coordination between the detrusor and the external bladder sphincter may get support from several levels, because before a cure was achieved, there seem to exist both coordination patterns, the synergia and the dyssynergia. Within the system theory of pattern formation (78,81), the coordination possibilities of synergia and dyssynergia can be understood as two micturition patterns with certain stabilities. With the improvement of bladder function a repair stage is passed at which the synergia and the dyssynergia patterns co-existed (86). The further repair consisted in the increase of the stability of the synergia pattern. For this important repair step in that patient some supraspinal control was necessary, which was established by limited regeneration of the spinal cord.

Control group

A typical control for the humans with spinal cord injuries may be a healthy human, which is operated under very light Propofol-anesthesia (pain may still partly be present). Such controls are not available. A brain-dead human may perform leg movements upon touch following 1 to 2 weeks of brain-death. It may therefore be that in fresh brain-dead humans a partial spinal shock is present. On the other hand, patients which undergo supraspinal CNS operations, which are not in connection with micturition (for example cancer operations), have no bladder function for 1 to 2 days following the operation (partial spinal shock?). Therefore a fresh brain-dead human is probably a reasonable control, even though extremely difficult to have excess to.

Also, the activity increase of the SP2 fibre of the HT6, due to parasympathetic spindle activation, has a similar time course as the bladder pressure increase of paraplegics following electrical ventral root stimulation for several seconds with 30 Hz (direct detrusor stimulation) in the operation.

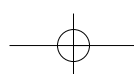
Safety in splitting multi-unit recordings into single-unit impulse patterns

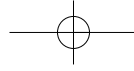
Single-fibre APs should have same shape and size, if the base line is straight and if the interspike intervals are longer than the refractory period. But firstly, APs may fall sometimes into the partial refractory period, so that the AP amplitude is reduced. Secondly, APs of small thin myelinated fibres (γ -motoneurons, preganglionic parasympathetic fibres, mucosal afferents,...), which have a long duration and a small AP amplitude (see Figure 3 of (83)), may change the base line (like large noise), even though the individual AP wave forms cannot be recognized. Activity of parasympathetic fibres and γ -motoneurons will have been present and will have added up with the spindle afferent activity. Therefore the single unit shape varies.

The APs of the bursts of the single spindle fibres in Fig. 11d,e were recognized by similar wave forms on both traces and same conduction times and marked by arrows. One or two APs were unsafe. Because of base line changes, the single fibre APs are not identical on the same trace. The APs of a single fibre on the two traces are anyway different because of the different recording conditions at the two electrode pairs. In principle it is possible that the APs of several fibres have accidentally an occurrence on trace 'a' which looks like a burst firing from a single unit. Such an occurrence is extremely seldom, whereas the burst firing often occurred. Further, the conditions for the time matching are different on trace 'b' from the 10 mm distant electrode pair; the pattern will be different there. Actually the second electrode pair is the power in the method of splitting multi-unit recordings into single-unit patterns. A third electrode pair could give even more safety in splitting.

Automatic bladder, hyperreflexia and dyssynergia of the bladder

The by the parasympathetic division activated secondary muscle spindle afferents showed different firing patterns. The activity level changes of the spindle afferents, measured intra-operatively, were similar to the active detrusor pressure changes upon retrograde bladder filling, measured pre-operatively. It





seems therefore as if the detrusor pressure gives information about the functional stage of the highly activated parasympathetic division. Low level parasympathetic activation, which can probably be measured by the doublet firing of the secondary spindle afferents cannot be judged by the detrusor activation. Since there are several kinds of too early detrusor activation (hyperreflexia), there are probably several kinds of dysfunction of the parasympathetic division.

Even though a hyperreflexia of the bladder (to early detrusor activation, generalization of the adequate afferent input (see below)) and a dyssynergia of the bladder (simultaneous activation of detrusor and ext. sphincter) were present in the 3 examined paraplegics, they must not necessarily accompany each other. The 3 paraplegics had a complete spinal cord injury well above the lumbosacral cord and below the brain stem; they all had an automatic bladder that means, the detrusor was activated involuntary with retrograde bladder filling and the activation could not be stopped on volition. All patients had a hyperreflexia of the bladder that means, the detrusor was activated for too small filling volumes. There are mainly 2 kinds of hyperreflexia: a spot like too early activation of the detrusor (Fig. 6, para 9) and a plateau-like undulating-like (up to several minutes) activation (cystometry not shown, para 11). In hyperreflexia, the detrusor cannot be activated by bladder afferent activity only. Touching, tapping or manipulating the skin of the perineum, of the Head's zone of the bladder (dermatomes TH12-S1) or of the penis (not accompanied by a penial erection) may activate the detrusor. Paraplegics with incomplete spinal cord injuries may have a hyperreflexia of the bladder, but no dyssynergia. On the other hand there are paraplegics with a dyssynergia of the bladder, but they have no hyperreflexia (similar to para 5).

The 3 examined cases are therefore somehow characteristic cases. All 3 paraplegics had a clinical complete spinal cord injury (few functioning tract fibres could be spared) and (therefore) a dyssynergia of the bladder. Para 9 and 11 had additionally a hyperreflexia of the bladder. In para 9 the detrusor was spot-like activated and in para 11 plateau-undulating-like. How much the different detrusor activation correlates with the parasympathetically induced secondary muscle spindle activity changes, has fur-

ther research to show. Since all spinal cord injuries are different, the lesion-induced changes of the nervous system will show delicate equilibriums (65). It seems possible to explore the human nervous system by detailed analyses of the lesion-induced changes of different paraplegics.

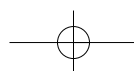
In the previous paper (83) it was found that in patients with a hyperreflexia of the bladder, the urinary bladder stretch (S1) and tension receptor afferent (ST) activity levels were undulating and increased. It was proposed that receptor field signal transduction mechanisms of bladder afferents had changed. The hyperreflexia of the bladder can therefore be explained by the changed afferent input from the bladder and other receptors of the urogenital domain and a probable changed processing of the afferent input in the spinal cord.

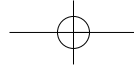
With respect to human electrophysiology, the detrusor-sphincteric dyssynergia is probably due to a disconnection from the pontine micturition centre and/or a pathologic interaction between the somatic and the parasympathetic divisions, which has in terms of system theory of pattern formation (81) the consequence that the stability of the dyssynergia pattern is too high (the potential well too deep) in comparison to that of the synergia pattern (86). Further, the attractors for the synergia and the dyssynergia patterns are probably of unphysiologic form in the attractor layout.

Clinical implications: some history

It has been reported that a neonatal somatovesical reflex in adult cats can be unmasked with the serotonin autoreceptor antagonist 5-MeODMT (75) and that delta opiod receptors regulate reflex pathways to the bladder, whereas kappa opiod receptors regulate reflex pathways to the sphincters (67). This differential regulation of bladder and sphincter pathways suggests possible means for the pharmacological management of urine retention and/or incontinence.

Pharmacological intervention is of importance following spinal cord injury in human, since disorders of the spinal cord can be of such strength, that even joints may dislocate. If on the other hand, paraplegics don't want to reduce their life expectation times by the side effects of drugs and want to regain





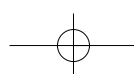
a higher quality of life especially in severe cervical spinal cord injury; other treatments have to be found and are found (86). Also, drugs may hinder the reorganization and regeneration of the spinal cord. The geographical landscape of neuroattractive gradients during endogenous stem cell therapy (81,82,86), induced by coordination dynamics therapy, may be disturbed with the consequence that the homing of cells and connections becomes impaired.

Spontaneous healing of human spinal cord injury has not been observed so far. Since nerve cells are not able to divide spontaneously in the adult, the CNS seems to recruit other nerve cells to take over for destroyed ones. The substitution of a function from other parts of the CNS is only possible if the necessary connections exist or can be built and if there is enough plasticity in the human CNS for relearning the functions. In spinal cord injuries nerve cells and tracts are destroyed. Injuries of the tracts are worse since the caudal spinal cord is disconnected from supraspinal control. Tract cells regenerate only over small distances, are impeded by scar tissue formation and form inappropriate synapses (for references see (56)). The normal surgical strategy to cut unhealthy tissue away and substitute nervous tissue (embryonic) is not feasible. Firstly, only few spinal cord injuries are complete. Resection of the damaged spinal cord parts would destroy still existing tract fibres. Secondly, by cutting the damaged spinal cord, e.g. in the lumbal range the caudal spinal cord will be disconnected from the blood supply and also die, because 70% of blood is supplied via the largest feeder artery (Adamkiewicz) and is distributed via the longitudinal trunks (45). Replacement of damaged spinal cord tissue by embryonic nervous tissue in animals is of interest for the study of the mechanism of regeneration, but had no consequences so far for the reconstruction of functions in humans. The injection of different kinds of stem cells had also so far no consequences for the repair of the injured spinal cord in human. World wide performed stem cell therapies are doubtful because of missing scientific publications and necessary diagnostics and doubtful theory (81). The therapeutic potential of neural stem cells has recently been reviewed (76). A qualified study by the author on stem cell therapy and coordination dynamics therapy on a patient with a thoracic spinal cord injury was not successful (79,80). For discussions of

stem cell therapies and literature see Refs. 80,81. Stem cell therapies are still in the experimental stage.

Since the damaged spinal cord part cannot be removed, neurosurgeons use to bypass it by performing a nerve anastomosis from the lower intercostal nerves rostral to the level of injury to the cauda equina nerve roots caudal to the lesion. Regeneration occurs, but no useful functions are obtained. In the most advanced operation (11), the regeneration of the urinary bladder function could be obtained, but the detrusor and the sphincter contracted simultaneously. At the beginning of this research project the author also tried to improve such nerve anastomosis, so that the patients get useful functions reconstructed (49-52). The number of total nerve fibres, of afferents and efferents of the donor nerves has to be compared with the acceptor nerves. E.g., it is useless to try to reinnervate the lower human body on one side with one intercostal nerve, which contains 10,000 myelinated fibres, if 250,000 are needed. However, the number of myelinated fibres of one intercostal nerve is sufficient for regeneration of the urinary bladder. Mismatch and functional aspects have to be taken into consideration. To make a separate function of the detrusor and the sphincter possible, the bladder has to be reinnervated by the two different motoneuron pools, present in the intercostal nerve distal to its branching into two skin nerves (nervus cutaneus lateralis), a pure muscle branch supplying the musculus obliquus externus abdominis and the mixed nerve running to the musculus rectus abdominis. Specific bladder afferents can be reconstructed by using the skin afferents from the Head's zone (ramus cutaneus anterior of the intercostals T12 to S1). For further details see (49-52,56). The author did not proceed further with this nerve anastomosis therapy, since firstly it is still a partial destructive operation, secondly the patients need more than a functioning bladder, and thirdly in cervical spinal cord injuries this anastomosis cannot be performed.

It has been reported that in adult rats axonal regeneration after partial cord transection is greatly increased by blocking a subset of inhibitory myelin-associated proteins with neutralizing antibodies (61). It has then been discussed with respect to human applicability that it is "just" a question of making it work (7). In a recent review article on the repair of spinal cord injury in the same journal,



12 years later (77), it is still “just” a question of making it work. Human research is not included in the review. The enhanced regeneration of corticospinal tracts of the treated rats has been demonstrated by an enhancement of regenerating axons in the not lesioned cord and by the improved running. It has not been proven electrophysiologically that the corticospinal tract fibres and the formed synapses were functioning. It has also been reported that late-growing axons are able to take an aberrant rout (8). Still, the improved running of the treated rats is difficult to understand. Sperry transposed the nerve supplies of flexor and extensor muscles in rat (63) and monkey (64): the monkey relearned the task after some time, the rat did not. Surprisingly few trials were required for poliomyelitis patients to use transposed tendons successfully (73). When cutting in experimental rats only 50% of the spinal cord, the repair results have no consequences for the regeneration of the human spinal cord, because firstly the rat has a higher capacity for regeneration and secondly it has been shown in a human patient with a 50% injured spinal cord (according to magnetic resonance imaging), that movement and bladder functions could be repaired by a mainly functional regeneration induced by coordination dynamics therapy (81). Further, with respect to the nerve anastomosis from the lower intercostal nerves to the cauda equina nerve roots, nerve fibres of the intercostal nerves reinnervated the urinary bladder, but useful functions were not obtained (11). Something like 20 years were not enough time, “just” to make this nerve anastomosis work.

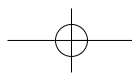
In the human nervous system the regenerative capacity is poor, but the learning-induced plasticity seems to be extremely high. A near-total functional recovery was achieved in a patient with an incomplete spinal cord injury after 3 years of coordination dynamics therapy (81). Even in severe cervical spinal cord injury with a 95% injured spinal cord (according to magnetic resonance imaging) a partial cure is possible if coordination dynamics therapy is administered (82,85,86). The training and learning-induced plasticity of the human CNS has by far been underestimated.

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