Invited Review

Central nervous control of micturition and urine storage

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Abstract

The micturition reflex is one of the autonomic reflexes, but the release of urine is regulated by voluntary neural mechanisms that involve centers in the brain and spinal cord. The micturition reflex is a bladder-to-bladder contraction reflex for which the reflex center is located in the rostral pontine tegmentum (pontine micturition center: PMC). There are two afferent pathways from the bladder to the brain. One is the dorsal system and the other is the spinothalamic tract. Afferents to the PMC ascend in the spinotegmental tract, which run through the lateral funiculus of the spinal cord. The efferent pathway from the PMC also runs through the lateral funiculus of the spinal cord to inhibit the thoracolumbar sympathetic nucleus and the sacral pudendal nerve nucleus, while promoting the activity of the sacral parasymapathetic nucleus. Inhibition of the sympathetic nucleus and pudendal nerve nucleus induces relaxation of the bladder neck and the external urethral sphincter, respectively. There are two centers that inhibit micturition in the pons, which are the pontine urine storage center and the rostral pontine reticular formation. In the lumbosacral cord, excitatory glutamatergic and inhibitory glycinergic/GABAergic neurons influence both the afferent and efferent limbs of the micturition reflex. The activity of these neurons is affected by the pontine activity. There are various excitatory and inhibitory areas co-existing in the brain, but the brain has an overall inhibitory effect on micturition, and thus maintains continence. For micturition to occur, the cerebrum must abate its inhibitory influence on the PMC.

Key words: bladder, micturition, nervous system, urethra, urine storage

Introduction

Fish have small bladders, while amphibians and mammals use the bladder as a reservoir for storage and periodic release of urine. The bladder is unique with regard to its myogenic properties as well as the complexity of its extrinsic neural regulation. The bladder wall is permeable to water and the degree of permeability is similar in many species, including humans

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(Fellows and Marshall, 1972). In rats, absorption of water through the bladder wall occurs when the intravesical volume is equal to or greater than that evoking the micturition reflex (Sugaya *et al.*, 1997), and the amount absorbed depends on the intravesical surface area (Fellows and Marshall, 1972) or intravesical water volume (Hilson *et al.*, 1990; Sugaya *et al.*, 1997). However, the bladder is not only permeable to water, but also to electrolytes, creatinine, and urea, which are harmful to the body (Au *et al.*, 1991; Calamita *et al.*, 1991; Harris *et al.*, 1992; Levinsky and Berliner, 1959; Parsons *et al.*, 1991). Therefore, the micturition reflex may act to limit the reabsorption of water and other substances by controlling the duration of exposure of the bladder epithelium to urine. The micturition reflex is one of the autonomic reflexes, but the release of urine is regulated by voluntary neural mechanisms that involve centers in the brain and spinal cord (Steers, 1998). Although neural input plays a role in maintaining continence, urine storage also relies on the viscoelastic and myogenic properties of the bladder and urethra. Because of this complex system of myogenic and neurogenic regulation, the bladder and its outlet are exquisitely sensitive to metabolic disorders, neurological disease, trauma, and drugs (Steers, 1998). This review integrates recent advances in neurophysiology and neuropharmacology with basic and clinical studies on the central nervous control of micturition and urine storage.

Characteristics of bladder smooth muscle

The bladder is largely composed of smooth muscle cells. One of the characteristics of smooth muscle cells is that contraction occurs when these cells are stretched. This characteristic of smooth muscle cells may contribute to involuntary peristalsis of the gut or ureter. However, the bladder does not contract involuntarily in healthy adults, even when it is filled with urine. This is due to the small number of cell-to-cell connections (gap junctions) between the smooth muscle cells in the bladder (Steers, 1998). Bladder smooth muscle cells actually do contract when stretched, but these contractions do not occur synchronously, so the bladder as a whole seems to be silent (Sugaya and de Groat, 2000). Desynchronization may facilitate the voluntary control of bladder function. However, in patients with an obstructed bladder, which often occurs due to benign prostatic hyperplasia, the number of gap junctions between the smooth muscle cells increases, and the bladder may become unstable (Christ *et al.*, 2003; Haefliger *et al.*, 2002; Haferkamp *et al.*, 2004; Miyazato *et al.*, 2005b).

Anatomy and innervation of the lower urinary tract

Micturition and urine storage depend on coordinated action between two functional units in the lower urinary tract, which are (a) a reservoir (the urinary bladder) and (b) an outlet (the bladder neck and the smooth and striated muscle of the urethra) (Andersson, 1993; de Groat *et al.*, 1993; de Groat and Yoshimura, 2001; Yoshimura and de Groat, 1997). During voiding, the muscles at the bladder outlet relax and the bladder smooth muscle contracts, raising the intravesical pressure and inducing urine flow. During urine storage, the bladder outlet is closed and the bladder smooth muscle is quiescent, allowing the intravesical pressure to remain low

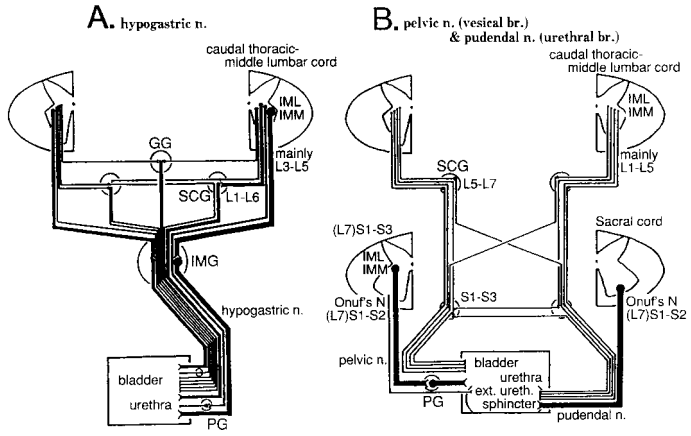

Fig. 1. Peripheral efferent neural pathways innervating the lower urinary tract in the cat. A. Hypogastric nerve. The hypogastric nerve contains sympathetic preganglionic fibers that project to the pelvic ganglions (PG) and postganglionic fibers that originate from the sympathetic chain ganglions (SCG), gonadal ganglions (GG), or inferior mesenteric ganglions (IMG). These sympathetic preganglionic fibers are derived from the intermediolateral and intermediomedial nuclei (IML and IMM) located between the caudal thoracic cord and middle lumbar cord. B. Pelvic nerve (vesical branch) and pudendal nerve (urethral branch). The vesical branch of the pelvic nerve contains sympathetic postganglionic fibers originating from the SCG, parasympathetic preganglionic fibers innervating the PG, and somatic fibers that originate from Onuf's nucleus (the pudendal nerve nucleus) and innervating the external urethral sphincter. These parasympathetic preganglionic fibers are derived from the IML and IMM in the sacral cord. The urethral branch of the pudendal nerve contains sympathetic postganglionic fibers originating from the SCG, and somatic fibers originating from Onuf's nucleus located in the ventrolateral region of the sacral cord. From Sugaya *et al.* (1988a).

over a wide range of bladder volumes. These changes are coordinated by three sets of nerves (parasympathetic, sympathetic, and somatic) that emerge from the sacral and thoracolumbar spinal cord (Andersson, 1993; de Groat *et al.*, 1993; Yoshimura and de Groat, 1997) (Fig. 1). Sacral parasympathetic (pelvic) nerves provide excitatory inputs (cholinergic and purinergic) to the bladder and have an inhibitory (nitrergic) effect on the urethra (de Groat *et al.*, 1993; Ralevic and Burnstock, 1998). Thoracolumbar sympathetic pathways release noradrenaline and provide excitatory inputs to the bladder neck and the urethra, as well as both facilitatory and inhibitory inputs to parasympathetic ganglia, and, in some species, have an inhibitory effect on bladder smooth muscle (Andersson, 1993; de Groat *et al.*, 1993). These sympathetic pathways mainly run through the hypogastric nerves, as well as partly in the pelvic and pudendal nerves, after leaving the sympathetic nerve trunks (Sugaya *et al.*, 1988a). The lumbosacral efferent pathways in the pudendal nerves provide cholinergic excitatory inputs to the striated muscle of the urethral sphincter.

Afferent activity in the bladder and urethra is conveyed to the central nervous system by three sets of nerves (de Groat *et al.*, 1993; Yoshimura and de Groat, 1997; Morrison, 1999). The most important afferents for initiation of micturition are those passing through the pelvic nerves to the sacral cord. These afferents consist of small myelinated (A-delta) fibers and unmyelinated

(C) fibers, which convey impulses from tension receptors, volume receptors, and nociceptors in the bladder wall (de Groat *et al.*, 1993; Yoshimura and de Groat, 1997; Morrison, 1999). Afferent nerves are located in the serosa and the muscle layer as well as adjacent to and within the epithelial lining (urothelium) of the bladder and urethra (Morrison, 1999; Smet *et al.*, 1997). Epithelial afferents can respond to changes in the composition of the urine or to chemical mediators [nitric oxide (NO), prostaglandins, and adenosine triphosphate (ATP)] released from urothelial cells (Downie and Karmazyn, 1984; Ferguson *et al.*, 1997; Morrison, 1999; Namasivayam *et al.*, 1999; Pinna *et al.*, 1999). Electrophysiological studies performed in cats have shown that A-delta bladder afferents respond in a graduated manner to passive distension of the bladder as well as active contraction (Morrison, 1999), and therefore trigger the sensation of bladder filling. C-fiber bladder afferents appear to function primarily as nociceptors (Maggi, 1993) and are normally not mechanosensitive (*i.e.*, silent C-fibers), but can be activated by noxious stimuli (Morrison, 1999). In the rat, A-delta fibers and some C-fiber afferents are mechanosensitive (Smet *et al.*, 1997).

Pontine micturition center and the micturition reflex pathway

A total of 12 reflexes involved in the release of urine or urine storage have been reported (Mahony *et al.*, 1977). Although many of these are spinal reflexes that maintain the release of urine or urine storage, the reflex evoking micturition is the bladder-to-bladder micturition reflex for which the reflex center is located in the rostral pontine tegmentum (pontine micturition center) (Barrington, 1925; de Groat *et al.*, 1993; Kuru, 1965) (Fig. 2).

The pontine micturition center (PMC), where electrical stimulation evokes micturition, corresponds to the nucleus locus coeruleus alpha (LCa) in the cat (Sugaya *et al.*, 1987a) and the dog (Nishizawa *et al.*, 1988). Neurons in the LCa show an increased firing frequency during the voiding phase or collecting phase, but LCa neurons projecting axons to the spinal cord only increase firing during the voiding phase in cats (Sugaya *et al.*, 2003b) (Fig. 3). There are many noradrenergic neurons in the LCa, and these neurons project axons to the spinal cord. In the rat, the PMC corresponds to Barrington's nucleus, which is located near the nucleus locus coeruleus (Sugaya *et al.*, 1998; Swanson, 1992). However, there are no noradrenergic neurons in Barrington's nucleus. Microinjection of glutamate (Mallory *et al.*, 1991), carbachol (a cholinomimetic agent), acetylcholine, noradrenaline (Sugaya *et al.*, 1987a; 1988e), naloxone (Noto *et al.*, 1991), or bicuculline (a GABA antagonist) (de Groat *et al.*, 1993) into the PMC induces bladder contraction, decreases the threshold bladder volume that induces the micturition reflex, or increases the amplitude of bladder contraction. Microinjection of leucine-enkephalin (Sugaya *et al.*, 1988e) or fentanyl (Noto *et al.*, 1991) into the PMC shows a reversal effect. Therefore, the PMC may act as a switch in the micturition reflex pathway. This switch seems to regulate bladder capacity and bladder contraction pressure, as well as coordinating the activity of the bladder and the urethral sphincter.

Among the pathways involved in bladder sensation or a desire to void, there are two afferent pathways from the bladder to the brain. One is the dorsal system, in which primary afferent fibers from the bladder pass directly through the dorsal funiculus of the spinal cord and project

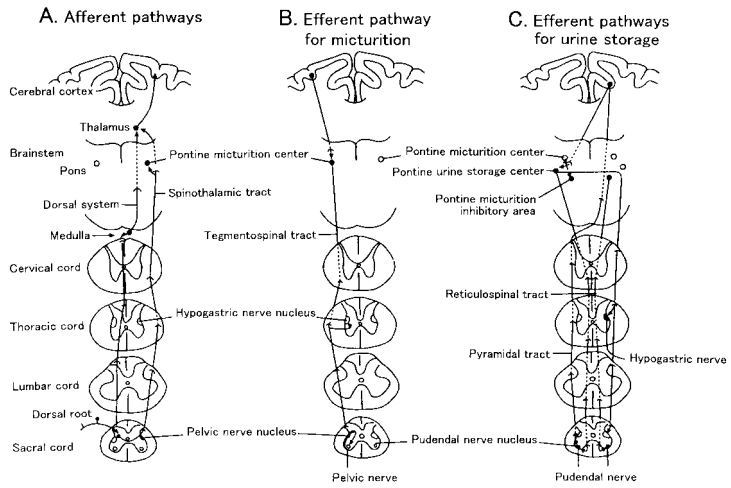

Fig. 2. Central afferent and efferent neural pathways for bladder sensation, micturition, and urine storage. A. Afferent pathways. There are two afferent pathways that convey bladder sensation: the dorsal system and the spinothalamic tract. An afferent limb of the micturition reflex pathway runs in the spinotegmental tract, which may be a collateral of the spinothalamic tract. B. Efferent pathway for micturition. There is one essential efferent pathway for micturition that arises from the pontine micturition center (PMC). This pathway runs through the lateral funiculus of the spinal cord to inhibit the hypogastric (sympathetic) nerve nucleus and the pudendal nerve nucleus (Onuf's nucleus), while it excites to the pelvic (parasympathetic) nerve nucleus. The PMC receives projections from several areas of the cerebral cortex. C. Efferent pathways for urine storage. There are several efferent pathways that promote urine storage from the cerebral cortex, pontine urine storage center (PUSC), and pontine micturition inhibitory area (rostral pontine reticular formation; RPRF). The pyramidal tract from the cerebral cortex runs through the lateral funiculus of the spinal cord and innervates the external urethral sphincter. The descending pathways from the PUSC run through the ventral and contralateral lateral funiculi, while that from the pontine micturition inhibitory area (RPRF) runs through the ventral funiculus. The PUSC and RPRF also receive projections from several areas of the cerebral cortex that project to the PMC.

to the nucleus gracilis or nucleus cuneatus in the medulla (Morgan *et al.*, 1981; Sugaya *et al.*, 1988b; Ueyama *et al.*, 1984). The other is the spinothalamic tract, in which secondary afferent fibers from the lumbosacral cord pass through the lateral funiculus of the spinal cord and project to the thalamus (de Groat *et al.*, 1993). Afferents to the PMC run through the spinotegmental tract and may be collaterals of the afferents in the spinothalamic tract (Sugaya *et al.*, 1988c). Both afferent pathways, the dorsal system and the spinothalamic tract, convey impulses from the bladder to the thalamus and finally to the sensory areas of the cerebral cortex.

The efferent pathway from the PMC passes through the lateral funiculus of the spinal cord, inhibits the thoracolumbar sympathetic nucleus and the pudendal nerve nucleus (Onuf's nucleus) in the sacral cord, and excites the parasymapathetic nucleus in the sacral cord (Satoh, 1993; Sugaya *et al.*, 1988d). Inhibition of the sympathetic nucleus and pudendal nerve nucleus induces relaxation of the bladder neck (the internal urethral sphincter) and the external urethral

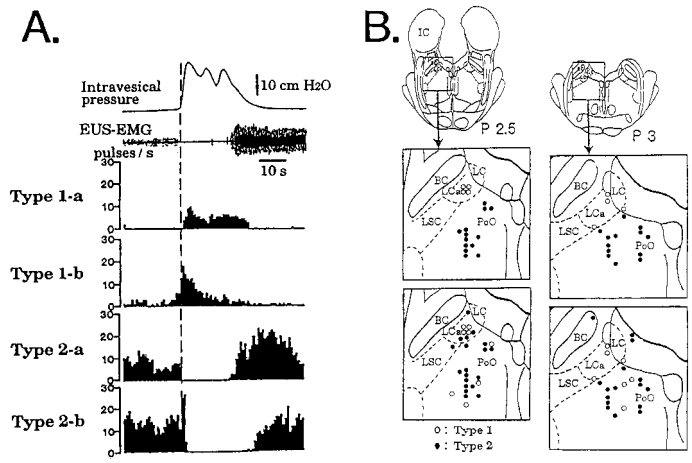

Fig. 3. Representative firing pattern and distribution of rostral pontine units in the cat. A. Representative firing pattern of pontine units during cystometry. Type 1 units (increasing type) are characterized by an increase of their firing frequency during the voiding phase that almost parallels the increase of bladder pressure (type 1-a). Type 1-b units show a rapid increase of firing at the onset of bladder contraction, followed by a gradual decrease. Type 1-a and type 1-b units are sometimes difficult to separate when the intravesical pressure increases rapidly at the onset of bladder contraction, followed by a gradual decrease. Type 2 units (decreasing type) are characterized by a decrease or cessation of firing during voiding (type 2-a). Some of these units show a rapid increase of firing at the onset of bladder contraction (type 2-b), followed by cessation of firing during voiding. Type 2-a and type 2-b units are also sometimes difficult to separate when the firing frequency increases gradually before bladder contraction. B. Distribution of rostral pontine units. The locations of type 1 and type 2 units are plotted in the lower frontal planes, while units activated antidromically by L1 stimulation are plotted in the upper planes. A total of 15 type 1 units and 35 type 2 units are scattered through the rostral pontine area. An antidromic response to L1 stimulation is shown by 8 type 1 units and 26 type 2 units located in the LCa or its border regions and in the PoO, respectively. P 2.5 and P 3 are Horsley-Clarke coordinates. BC, brachium conjunctivum; EUS-EMG, electromyogram of the external urethral sphincter; IC, inferior colliculus; LC, nucleus locus coeruleus; LCa, nucleus locus coeruleus alpha; LSC, nucleus locus subcoeruleus; PoO, nucleus reticularis pontis oralis. From Sugaya *et al.* (2003b).

sphincter, respectively (de Groat *et al.*, 1993).

The transmitter involved in the descending pathway from the PMC was thought to be noradrenaline or glutamate. Intrathecal injection of an adrenergic alpha-1 receptor antagonist was reported to inhibit bladder contraction induced by electrical stimulation of the PMC in anesthetized cats (Yoshimura *et al.*, 1987). However, intrathecal injection of such an antagonist did not influence bladder contraction in decerebrate dogs (Shimoda, 1994) or awake cats (Espey *et al.*, 1992). Intrathecal injection of a glutamate (NMDA or AMPA) receptor antagonist was shown to inhibit bladder contraction in anesthetized rats (Yoshiyama *et al.*, 1993), but was not effective in rats with spinal cord injury (Nishizawa *et al.*, 1999: Yoshiyama *et al.*, 1997) or decerebrate rats (Yoshiyama *et al.*, 1995). Therefore, the descending neurons from the PMC are still unknown. However, adrenergic or glutamatergic projections to the lumbosacral cord

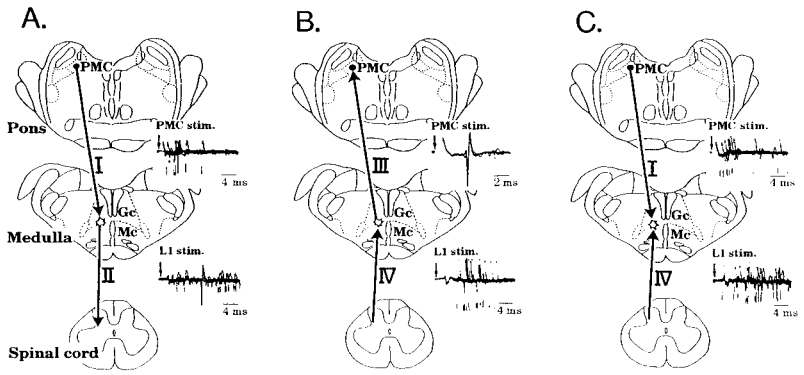

Fig. 4. Connections between the pontine micturition center (PMC) and the spinal cord via medullary neurons. Each photograph of medullary unit discharges shows the discharge in response to 10 stimulations (arrow) of the L1 or the PMC. Both type 1 and type 2 units are recorded in the nucleus reticularis gigantocellularis (Gc), and nucleus reticularis magnocellularis (Mc) of the medulla. I: neurons that only respond orthodromically to PMC stimulation (A, C); II: neurons that respond antidromically to L1 stimulation (A); III: neurons that respond antidromically to PMC stimulation (B); IV: neurons that only respond orthodromically to L1 stimulation (B, C); I + II: neurons that respond orthodromically and antidromically to PMC and L1 stimulation, respectively (A); III + IV: neurons that respond antidromically and orthodromically to PMC and L1 stimulation, respectively (B); I + IV: neurons that respond orthodromically to both PMC and L1 stimulation (C). L1, the first lumbar segment of the spinal cord; stim, stimulation. From Sugaya *et al.* (2003b).

influence the activity of the afferent and efferent limbs of the micturition reflex. For example, adrenergic projections to the lumbosacral cord activate adrenergic alpha-1D receptors in the afferent limb of the micturition reflex in rats, and thus promote the reflex (Sugaya *et al.*, 2002). In rats with chronic spinal cord injury, intrathecal injection of an adrenergic alpha-1D receptor antagonist inhibits bladder contraction (Sugaya and Nishijima, 2002). Clinically, patients with benign prostatic hyperplasia (BPH) and hypertension more often have urinary frequency than BPH patients without hypertension (Sugaya *et al.*, 2003a), while patients with nocturia have high serum catecholamine levels of compared to those without nocturia (Sugaya *et al.*, 2001). Therefore, it is possible that serum catecholamines may cross the blood-brain barrier and activate the afferent limb of the micturition reflex in the lumbosacral cord.

In our recent study performed on cats, some medullary neurons (especially neurons in the nucleus reticularis magnocelluralis (Mc)) responded antidromically or orthodromically to L1 stimulation, but responded in the opposite manner to PMC stimulation (Sugaya *et al.*, 2003b). These findings suggest the existence of ascending and descending pathways that run between the PMC and spinal cord via medullary neurons (Fig. 4). PMC (LCa) neurons also responded antidromically and/or orthodromically to L1 stimulation. Anatomical studies have revealed ascending and descending pathways that run between the LCa and the sacral spinal cord (Holstege *et al.*, 1986; Sugaya *et al.*, 1988c, d), between the LCa and the Mc (Sakai *et al.*, 1979; Sugaya *et al.*, 1988c,d), and between the Mc and the sacral cord (Holstege and Kuypers, 1982). Therefore, it appears that there are two descending pathways and two ascending pathways

which run between the PMC and the spinal cord, *i.e.*, a direct pathway and another via medullary neurons. Moreover, the activity of Mc neurons is higher and the conduction velocity of these neurons is faster compared with LCa neurons (Sugaya *et al.*, 2003b). In the medulla, there may be a power generation (driving) system of the micturition reflex pathway.

Pontine urine storage center and pontine micturition inhibitory area

The pontine urine storage center (PUSC) exists ventrolateral to the PMC (Kuru, M. 1965; Nishizawa *et al.*, 1987; Sugaya *et al.*, 1998). The PUSC corresponds to the nucleus locus subcoeruleus in rats, cats, and dogs (Figs. 2 and 3). Electrical stimulation of the PUSC inhibits bladder contraction and promotes the activity of the external urethral sphincter. Microinjection of carbachol, noradrenaline, or leucine-enkephalin into the PUSC produces an increase of bladder capacity, but the injection of GABA causes a decrease of both bladder capacity and urethral sphincter activity (Matsuzaki, 1990). However, microinjection of these agents into the PUSC does not influence the amplitude of bladder contraction. Neurons in the nucleus locus subcoeruleus project to the lumbosacral cord and the nucleus raphe magnus (Kohama, 1992), and electrical stimulation of the nucleus raphe magnus also inhibits bladder contractions (Sugaya *et al.*, 1998). There are many serotonergic neurons in the nucleus raphe magnus, and these neurons project to the spinal cord. Serotonergic projections to the lumbosacral cord are reported to inhibit micturition (Espey *et al.*, 1992; Espey and Downie, 1995). Therefore, dual pathways may run from the PUSC to the sacral spinal cord, both direct and via the raphe nuclei.

Electrical stimulation or injection of carbachol (a cholinomimetic agent) into the rostral pontine reticular formation (RPRF, also known as the nucleus reticularis pontis oralis: PoO) just ventrocentral to the PMC also inhibits bladder contraction in cats and rats (Sugaya *et al.*, 1987b; Kimura *et al.*, 1995; Nishijima *et al.*, 2005) (Figs. 2 and 3). Neurons in the RPRF project to the spinal cord and the nucleus reticularis gigantocelluralis (Gc), which is located in the rostrodorsal medulla (Kohama, 1992). Neurons in the Gc also project to the lumbosacral cord (Mori, 1989; Takakusaki *et al.*, 1994). Therefore, it seems that there are also two descending pathways running between the RPRF and the spinal cord, a direct pathway and one via neurons in the Gc. The activity of Gc neurons is higher than that of RPRF (PoO) neurons, and Gc neurons have a faster conduction velocity (Sugaya *et al.*, 2003b). In the medulla, there may also be a power generation (driving) system of the micturition inhibitory reflex pathway. The descending pathway from the RPRF projects to lumbosacral inhibitory glycinergic neurons (Nishijima *et al.*, 2005).

Spinal amino acid neurons and the micturition reflex pathway

In the spinal cord, there are excitatory glutamatergic neurons, inhibitory glycinergic neurons, and some GABAergic neurons (de Groat *et al.*, 1993; de Groat and Yoshimura, 2001; Miyazato *et al.*, 2003, 2004, 2005a). Glutamatergic projections to the lumbosacral cord promote the micturition reflex and stimulate glycinergic neurons (Sugaya *et al.*, 2000). Glycinergic/GABAergic projections to the lumbosacral cord inhibit the micturition reflex and also inhibit

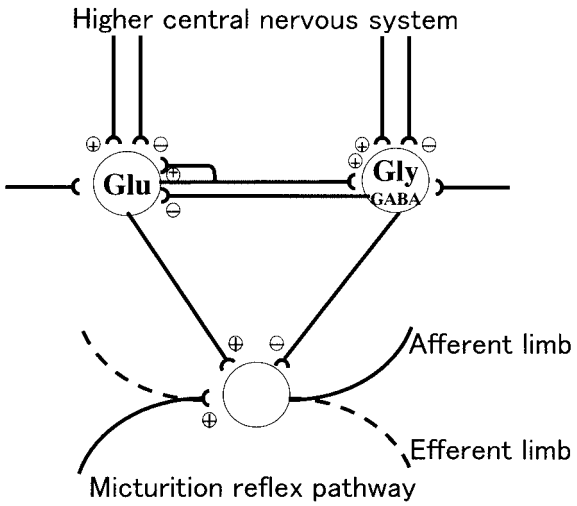

Fig. 5. Relationship between glutamatergic and glycinergic/GABAergic neurons and the micturition reflex pathway in the lumbosacral cord. Glutamatergic neurons (Glu) facilitate the afferent and efferent limbs of the micturition reflex, while glycinergic/GABAergic neurons (Gly GABA) inhibit the afferent and efferent limbs of the micturition reflex and also inhibit glutamatergic neurons. These glutamatergic and glycinergic/GABAergic neurons receive inputs from the higher central nervous system and also from peripheral afferent neurons.

glutamatergic neurons (Miyazato *et al.*, 2003) (Fig. 5). When the spinal cord is transected at the lower thoracic level, the lower extremities and bladder develop flaccid paralysis. At this time, the glycine level increases in the lumbosacral cord (Nishijima *et al.*, 2003a). In rats with chronic spinal cord injury, bladder activity increases and urinary frequency develops. At this time, the glycine level in the lumbosacral cord conversely shows a decrease. The changes of glycine in the lumbosacral cord after spinal cord injury are reflected by the serum glycine level with a delay of 1–2 weeks (Nishijima *et al.*, 2003a). On the other hand, cerebral infarction induces urinary frequency in rats and humans. At this time, the glutamate level decreases in the cerebrum of the rat, while the glycine level decreases in the brainstem, cervicothoracic cord, and lumbosacral cord (Nishijima *et al.*, 2003b). Two weeks later, urinary frequency improves and the glycine level recovers, but only in the lumbosacral cord. In rats with chronic bladder obstruction, a model of benign prostatic hyperplasia (BPH), the glycine level is decreased in the lumbosacral cord (Miyazato *et al.*, 2005b). The serum glycine level is decreased in both patients with BPH and rats with chronic bladder obstruction (Miyazato *et al.*, 2005b; Nishijima *et al.*, 2000). Therefore, bladder activity and glycinergic neuronal activity in the lumbosacral cord may show an inverse correlation, and glycinergic activity in the lumbosacral cord may perhaps be determined by measuring the serum glycine level. Dietary glycine (1–3%) inhibits bladder activity in rats with or without spinal cord injury, suggesting that glycine may be a useful agent for the treatment of overactive bladder (Miyazato *et al.*, 2005a).

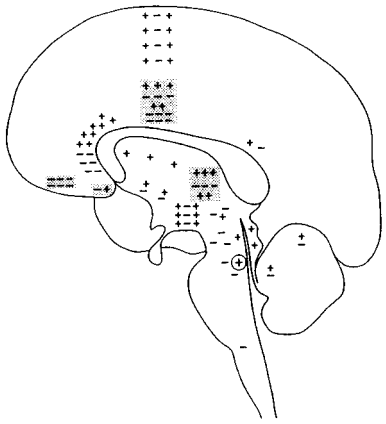

Fig. 6. Excitatory (+) and inhibitory areas (–) for micturition in the brain. There areas were determined by experiments involving electrical stimulation of the cat brain, and were plotted on the human brain. Finely dotted area shows the lateral and ventral aspects of the cerebral cortex and the amygdaloid body. There are many excitatory and inhibitory areas in the median, lateral, and ventral aspects of the frontal lobe. These excitatory and inhibitory areas are often located side by side. A plus inside a circle show the pontine micturition center.

Higher central nervous system (suprapontine) control of bladder function

Higher brain areas than the pons that influence the micturition reflex have been found in the cat by electrical stimulation. These include the cerebellum, periaquedactal gray in the midbrain, substantia nigra, red nucleus, thalamus, hypothalamus, amygdaloid body, and cerebral cortex (sensorimotor cortex, median or ventral aspects of the frontal lobe, *etc.*) (Gjone, 1966; Gjone and Setekleiv, 1963; Koyama *et al.*, 1962; Lewin *et al.*, 1967) (Fig. 6). These excitatory and inhibitory areas for micturition are often located side by side and many of these areas project to the PMC (Sugaya *et al.*, 1988c), PUSC, or RPRF (PoO) (Kohama, 1992). However, cerebral infarction due to occlusion of the internal carotid and middle cerebral arteries induces urinary frequency in rats (Nishijima *et al.*, 2003b; Yokoyama *et al.*, 1997). Decerebration above the level of the rostral pons decreases the bladder volume that evokes the micturition reflex in cats (Tang, 1955). In patients with cerebrovascular disease, urinary frequency and urgency are common (Steers, 1998). Therefore, the overall effect of the brain is to inhibit the micturition reflex.

There are both excitatory and inhibitory bladder-to-bladder, bladder-to-urethra, urethra-to-bladder, or urethra-to-urethra reflexes (Mahony *et al.*, 1977). When urine is being stored, these reflexes are set to promote storage. Some of the main switches for these reflexes are located in the pons, and some are in the spinal cord. The cerebral cortex exerts voluntary control and turns these switches on or off as needed (Fig. 7). The power generation system and execution (output) system for neural control are located in the medulla and the spinal cord (sacral cord), respectively. Since there are few connections between the PMC, PUSC, and RPRF in the pons, or between the Mc, Gc, and RM in the medulla, integration of the functions of these areas may

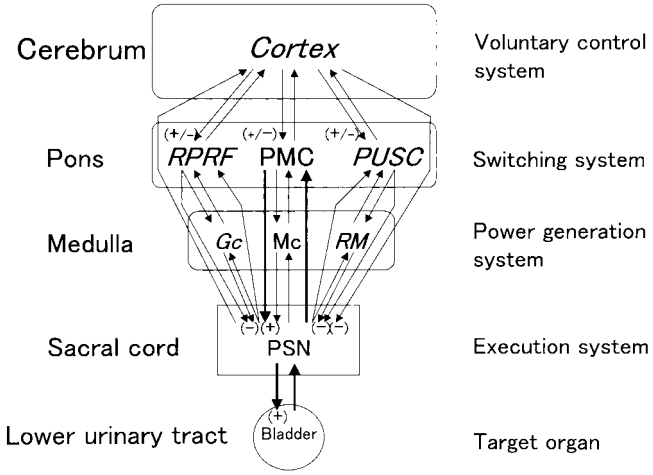

Fig. 7. Functional relationships among each part of the central nervous system involved in micturition and urine storage. There are micturition or urine storage switching systems (the PMC, PUSC, and RPRF) in the pons, and power generation (driving) systems (Mc, Gc, and RM) in the medulla. There are connections between the PMC and Mc, between the PUSC and RM, and between the RPRF and Gc, but there are few connections between the PMC, PUSC, and RPRF, or between the Mc, Gc, and RM. The cerebral cortex exerts voluntary control and turns the switches on or off as needed. Integration of the functions of each area is performed by the cerebrum and spinal cord, where the execution (output) system for the central nervous system is also located. Gc, nucleus reticularis gigantocellularis; Mc, nucleus reticularis magnocellularis; PMC, pontine micturition center; PSN, parasympathetic nucleus (pelvic nerve nucleus); PUSC, pontine urine storage center; RM, nucleus raphe magnus; RPRF, rostral pontine reticular formation.

be performed in the cerebrum and spinal cord. For micturition to occur, it seems that the cerebrum switches off the inhibitory projections to the PMC, as well as the excitatory projections to the PUSC and RPRF, and that activation of the micturition (bladder-to-bladder) reflex switches the other reflexes from the setting for urine storage to that for micturition.

Conclusion

Micturition is governed by several neural reflexes (Mahony *et al.*, 1977). These reflexes are inhibited at many levels, so that urine storage is maintained. The central nervous system is surrounded by the cerebrospinal fluid, and this fluid has a high GABA content (Manyam *et al.*, 1987). Since GABA is one of the inhibitory neurotransmitters, the brain and spinal cord are thought to be bathed in an inhibitory GABA pool. In fact, GABA has been reported to inhibit the micturition reflex (Igawa *et al.*, 1993; Miyazato *et al.*, 2004). In many mammals apart from humans, licking of the perineum of neonates by the mother induces micturition, and neonates cannot void without this licking (Sugaya and de Groat, 1994a; 1994b; 2002). This neonatal mechanism for inhibition of micturition is thought to maintain the water balance while the mother goes to find food, because the bladder mucosa is permeable to water (Fellows and

Marshall, 1972; Sugaya *et al.*, 1997). Thus, the micturition reflex is controlled by many inhibitory mechanisms, confirming that the nervous system essentially consists of reflexes and their inhibitory mechanisms, and that the function of urine storage is more important than micturition among bladder functions. During evolution, development of the bladder and mechanisms for urine storage may have been a major factor in amphibians coming ashore.

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