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Review article

Spinal pelvic-urethra reflex potentiation

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ABSTRACT

Spinal reflex potentiation (SRP) in the pelvic-urethra reflex activity is a form of activity-dependent neural plasticity, presumed to be essential for urethra contraction resulting continence under physiological conditions and also to underlie the pelvic pain caused by pathology in the pelvic cavity. Studies have demonstrated that SRP could be induced by electrical shocks, bladder distension and activation of the lumbosacral (L6-S1) spinal glutamatergic NMDA and AMPA receptors. Conversely, blockage of glutamatergic receptors using selective antagonists either attenuated or abolished the established SRP. Electrical shocks on and nicotine microinjection into the pontine tegmentum area facilitated SRP induction, but intrathecal serotonin antagonists abolished electrical stimulation- and nicotine-induced facilitation on SRP. Finally, the induction of SRP is highly estrogen-dependent, because surgical ablation of menstruation diminished the SRP which is prevented by estradiol supplements, and SRP is more significant in proestrus (high estrogen but low progesterone) than in metestrus (both estrogen and progesterone are low) of the menstrual cycle. We propose that SRP is relevant to urine continence under physiological conditions, and pathological facilitation of SRP could result in pelvic pain.

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1. Introduction

In the central nervous system (CNS), repetitive activation of synaptic connections could lead to strengthening of synaptic efficacy in a variety of brain structures [1–4]. In the CA1 area of the hippocampus, long-term potentiation (LTP) [5,6], a tetanization-induced enhancement in synaptic efficacy, has been investigated extensively in the last three decades, because it is considered a fundamental mechanism of learning and memory formation [4,7]. In addition, “windup”, a pain-related

synaptic plasticity, characterized by a progressive increase in evoked activity in the wide dynamic dorsal horn neurons, is presumed to underlie the development of allodynia and/or hyperalgesia [8,9].

2. Pelvic-urethra reflex potentiation

The pelvic-urethral reflex (PUR), in which sensory impulses induced by bladder distension transmit centripetally onto the

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dorsal horn neurons through the pelvic afferent fibers [10] and, after integrating within the spinal cord, motor impulses emerge via the pudendal efferent fibers, and therefore, cause external urethra sphincter contractions [11,12], has been shown to be essential for the urethra to develop sufficient resistance to maintain continence during the micturition cycle [13]. Spinal reflex potentiation (SRP) of the pelvic-urethra reflex was first reported in 2003, by demonstrating the firing of pudendal efferent nerves (PENs) and external urethra sphincter electromyogram (EUSE) evoked by pelvic afferent nerve (PAN) repetitive stimulation (RS, 1 stimulation/1 second), increased progressively following stimulation onset, then reached a plateau which was maintained until stimulation ceased. In contrast, PAN test stimulation (TS, 1 stimulation/30 seconds) evoked relatively constant baseline reflex activity with a single action potential [14]. Additionally, in parallel to inducing SRP, RS on PAN elongated the contraction wave of the urethra, implying the SRP of the pelvic-urethra reflex potentiation is physiologically relevant to urethra closure [14–16]. Moreover, stepwise saline distension of the urinary bladder from 0 to 4, 8, 12 and 16 mmHg dose-dependently potentiated TS-evoked baseline pelvic-urethra reflex activity, accompanied by elongation of the urethra contraction wave [17], suggesting physiological challenges, such as bladder distension, could induce SRP. Finally, during the early storage stage of a voiding cycle, negligible increments in intravesical pressure did not induce background spontaneous firing in EUSE, whereas, off-line analysis demonstrated that TS-evoked pelvic-urethra reflex activities were potentiated in parallel with intravesical pressure increases during this stage [17], suggesting that the strength of the pelvic-urethra reflex fluctuates following the micturition cycle. Together, these results imply that SRP could be a physiological phenomenon which occurs under physiological conditions.

3. Involved neurotransmission

Investigations using spinal administration of test agents demonstrated that SRP caused by repetitive electric shocks [18–25], bladder saline distension [17], rhythmic voiding cycle [22] and noxious visceral irritation [23–31] is blocked by intrathecal application of 2-amino-5-phosphono-valerate (APV), a glutamatergic NMDA receptor antagonist, and diminished by 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione (NBQX), a glutamatergic AMPA receptor antagonist. Conversely, spinal administration of NMDA and AMPA both provoke reflex potentiation in TS-induced baseline reflex activity [23–30], indicating crucial roles of spinal glutamatergic NMDA and AMPA receptor subtypes in the induction of PUR potentiation.

4. Descending control

Researchers investigating the possible areas exhibiting descending control on the SRP, have revealed that at the dorsal pontine tegmentum (DPT), synchronized electrical shocks to PAN stimulation facilitated RS-induced SRP. Spinal

administration of serotonin antagonist and high level spinal cord transaction at T1 level both abolished the facilitation on SRP caused by DPT stimulation [18,32]. In another study, microinjection of nicotinic agonist to the DPT, exhibited similar facilitatory effects on SRP as synchronized electric shocks did, and conversely, pharmacological blockage of the nicotinic cholinergic receptors (nACh) in this area abolished the modulation exhibited by the nicotinic agonist [33,34]. Additionally, the nicotinic agonist-induced facilitation on SRP was also blocked by intrathecal serotonin antagonist and T1 level spinal transaction [35]. Together these data suggest that activating nACh receptors at the DPT may modulate SRP induction via descending serotonergic neurotransmission.

5. Impacts of female gonadal hormones

Whether or not levels of circulatory estrogen affect lower urinary function through effects on SRP was first investigated using rats which received a sham operation (Sham), ovariectomy (OVX), or ovariectomy followed by estrogen supplementation (OVX + E). The magnitude of the RS-induced SRP and associated urethra contraction wave elongation decreased significantly in the OVX group, which was partially reversed by supplemental estrogen [15], indicating that estrogen impacts lower urinary function through modulating SRP. Moreover, by recording the evoked reflex activity in rats in different estrus stages of the female cycle, studies have shown noxious visceral stimulation induced SRP in both the proestrus and metestrus stages. However, the degree of reflex potentiation was significantly higher in the proestrus rats than the metestrus ones [31], implying that the strength of the SRP fluctuates in response to estrogen levels across different estrus stages. In addition to genomic actions mediated by nucleus receptors, administration of 17 β -estradiol (5 μ g/kg) was demonstrated to acutely facilitate noxious visceral stimulation-induced SRP which was reversed by intrathecal pre-treatment with ICI 182780, a non-selective membrane estrogen receptor antagonist [28], indicating a role of membrane estrogen receptor on the estrogen-dependent facilitation of SRP.

In addition to estrogen, a regimen of daily progesterone for 4 days attenuated RS-induced SRP and simultaneously regulated the expression of GABA_A receptor alpha 2, alpha 3, alpha 4 and delta subunits in ovariectomized rats. Finasteride, an antagonist of neurosteroid synthesis from progesterone, but not RU486, a progesterone receptor antagonist, reversed the progesterone-dependent inhibition of SRP. Moreover, SRP was attenuated after a short intrathecal treatment with the neurosteroids, allopregnanolone and 3 α ,5 α -tetrahydrodeoxycorticosterone (THDOC). Acute intrathecal administration of the GABA_A receptor antagonist bicuculline reversed the inhibition produced by progesterone, THDOC and allopregnanolone. These results imply that, through its metabolic neurosteroid, progesterone inhibits SRP by exerting effects on spinal GABA_A receptor expression [27]. This proposal is further supported by a study that showed progesterone, as well as two of its 3 α ,5 α -derivatives, allopregnanolone and THDOC, is capable of producing acute GABA_A receptor-dependent inhibition of SRP.

6. Possible role in urethral spasms

To investigate the rationale that anal stretch could relieve the high urethral resistance in neurogenic bladder or detrusor-sphincter dyssynergia, the impact of acute anal stretch on PUR potentiation was examined in urethane-anesthetized rats. Acute anal stretch using a mosquito clamp with a distance of 4 mm exhibited no effect, whereas distances of 8 mm attenuated and 12 mm abolished the repetitive stimulation-induced SRP. Intrathecal pretreatment with bicuculline, a GABA_A receptor antagonist, but not hydroxysaclofen, a GABA_A receptor antagonist, counteracted the anal stretch-dependent abolition of PUR potentiation [36]. These results suggested that GABAergic neurotransmission is an important spinal mechanism involved in inhibition of reflexive external urethra sphincter activity. Moreover, acute manual anal stretch, a maneuver that activates the spinal GABAergic system, may be used as an adjunct to assist voiding dysfunction in patients with overactive urethral sphincters.

7. Conclusion

The induction of spinal reflex potentiation in the pelvic-urethra reflex activity seems to be physiologically relevant to urethra closure, and pathologically relevant to pelvic pain. Therefore, its underlying mechanisms could provide information for developing a therapeutic strategy for neurogenic pelvic pain.

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