Neuronal nicotinic receptors: filling the void

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EFFORTS DURING THE PAST SEVERAL YEARS have enabled an enhanced level of understanding of urinary bladder physiology and pathophysiology, with continued exploitation of muscarinic receptors as drug targets, and the identification of novel molecular underpinnings of pathways such as C fiber afferents and the vanilloid TrpV1 receptors, the noncholinergic nonadrenergic mechanisms and P2X receptors (P2X1, P2X3), urothelial TrpV1 receptors, the noncholinergic nonadrenergic mechanisms and P2X receptors (P2X1, P2X3), urothelial signaling processes, and the central mechanisms of control of micturition involving diverse transmitter systems. The findings reported in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology by Lee and coworkers (9) now provide valuable insight into a potential role of neuronal nicotinic ACh receptors (nAChRs) in the central control of voiding function.

Micturition is a complex process requiring coordination of autonomic, somatic, and central nervous system pathways that involve bladder urothelium, ganglionic, spinal, and supraspinal mechanisms. The innervation of the urinary bladder by sacral parasympathetic and sympathetic nerves controls the voiding and the filling phases of micturition. Specifically, the sacral parasympathetic system provides excitatory input to the bladder and inhibitory input to the urethra, whereas the thoracolumbar sympathetic nerves provide excitatory input to the urethra and bladder neck and both excitatory and inhibitory inputs to the parasympathetic ganglia (7). nAChRs are known to play an integral role in the control of bladder function as mediators of fast synaptic transmission in both the parasympathetic and sympathetic autonomic ganglia (5). These receptors, located throughout the central and peripheral nervous system (10), are assembled from a family of at least 12 distinct subunits, α2-α10 and β2-β4, and function as homomers of a single subunit (such as α7), as simple heteropentamers as one type of α-subunit and one type of β-subunit (such as α4β2-receptors), and as complex heteropentamers of three or more subunits (such as α3α5β4-receptors). In contrast to the neuromuscular junction (α1β1γ), diverse nAChR subtypes predominate in the brain (α4β2, α7, etc.) and the autonomic nervous system (e.g., α3β4). The observed multiorgan autonomic dysfunctions in mice lacking the α3 alone or β2β4 combinations points to the involvement of nAChRs containing these subunits in the autonomic control of end organs such as the urinary bladder (11, 12). Both β2β4−/− or α3−/− mice showed no sensitivity to nicotine in vitro and developed severe bladder distension within 2 days after birth, and those that survived displayed enlarged bladders, dribbling urination, bladder infection, and urinary stones. Peripheral nAChR-mediated control of autonomic function may also occur at the level of the neuroeffector junction; little information is, however, available on the subunit composition of nicotinic receptors expressed in the pelvic plexus and intramural ganglia of the bladder. Preliminary reports demonstrating expression of several nAChR subunit mRNAs in rat bladder urothelium have recently appeared (3).

Although peripheral nAChRs located in the autonomic ganglia containing the α3-subtype are generally considered as the primary peripheral mediators of bladder function, the role of nAChR subtypes in the central nervous system (CNS) controlling micturition is far less understood. Nonetheless, it is well appreciated that various transmitter pathways in the CNS play a major role in controlling voiding function and urine output through both afferent and efferent brain-spinal pathways. CNS regulation of voiding is complicated by the fact that reflex pathways that mediate bladder function are also under voluntary control. The pontine micturition center (PMC), an area of the rostral pontine tegmentum located in the brain stem, is thought to serve as a relay center receiving information from the periaqueductal gray (PAG), which becomes activated by spinal Aβ-bladder afferents and subsequently transmits back efferent information through the sacral cord to activate parasympathetic neurons so as to inhibit urethral sphincter motoneurons during voiding. Glutamatergic transmission from the PMC is considered essential in controlling the spinal efferent pathways that regulate autonomic control of voiding function. In turn, several other neurotransmitter systems can modulate glutamatergic transmission at the level of the PMC. Whereas GABA and enkephalins have an inhibitory effect, dopamine activates the PMC and ACh is thought to contribute to both excitatory and inhibitory synaptic activity (6). In the latter case, the role of cholinergic modulation is likely influenced by the type of cholinergic receptor present in the PMC or other nuclei involved in the CNS control of bladder function.

Lee et al. have now examined central nicotinic receptor pathways controlling micturition in the rat by evaluating (±)-epibatidine (2), a nonselective high-affinity neuronal nicotinic receptor agonist, originally isolated from the Ecuadorian frog, Epipedobatus tricolor, in...
aware and urethane-anesthetized rats on voluntary and reflex voiding function, respectively (9). The authors show that a small dose of the nAChR agonist epibatidine (0.1 μg) injected intracerebroventricularely increased voiding frequency in both awake and anesthetized rats, but without affecting voiding pressure, and that the inhibitory effect produced by epibatidine could be antagonized by pretreatment with the nicotinic antagonist chlorisondamine intracerebroventricularely. In contrast, a higher dose of epibatidine (1 μg) administered either intracerebroventricularly or intravenously evoked an excitatory effect on voiding, possibly through activation of ganglionic nAChRs, given the observation that intracerebroventricular chlorisondamine failed to block the augmented response. With intracerebroventricular epibatidine administration, the authors speculate that the higher dose may be capable of entering the systemic circulation or, alternatively, may activate lower affinity nAChRs located centrally to elicit excitatory effects on voiding function. Lee and colleagues also discuss the possibility that the inhibitory effect produced by (+)-epibatidine may involve the nAChR-mediated activation of descending serotonergic pathways in the brain stem, such as the nucleus raphe magnus, that modulate serotonin release in the spinal cord to increase bladder capacity, a mechanism also previously proposed as underlying the antinociceptive activities of nAChR agonists (4).

Several transmitter pathways in the CNS can modulate voiding function (1), but few drugs with a defined central site of action have been developed thus far for the treatment of voiding disorders. The observation that neuronal nAChRs may indeed modulate central control of voiding function and that pharmacological activation of nAChRs in the brain can inhibit voiding reflexes raises the possibility that nAChR agonists may have utility in treating neurogenic voiding dysfunction. However, because of the lack of pharmacological selectivity of (+)-epibatidine and chlorisondamine, the question of which nAChR subtypes are specifically involved in mediating central regulation of voiding function, and whether the latter activity can be disassociated from potential side effect liabilities will require further study. In this regard, preliminary studies using subtype selective agonists have begun to emerge (8). Future studies using selective agonist and antagonist tools could help elucidation of the subtype(s) involved and the mechanisms underlying central control of voiding function, which could ultimately set the stage for targeting distinct nicotinic receptor subtype(s) for the potential treatment of lower urinary tract symptoms.

REFERENCES