Mechanisms of Autonomic Drug Action on the Bladder Outlet

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Pharmacologic manipulation of the bladder outlet is a relatively new undertaking. Most of the currently used drugs have not been rationally developed or selected to specifically alter known physiologic processes in the lower urinary tract. On the contrary, the urinary tract effects of these agents have been recognized primarily through clinical observation of "side effects" in patients being treated for diseases of the cardiovascular, gastrointestinal, and central nervous systems. In fact, much of the current research interest in the neuroanatomy, neurophysiology, and neuropharmacology of the urinary bladder and its outlet was initiated by attempts to understand the basic mechanisms responsible for these "side effects." Many of these pharmacologic agents exert their effects by altering the function of the autonomic nervous system; these mechanisms of action are the subject of this chapter. Drugs that act by other means are discussed elsewhere.

Anatomic and Physiological Considerations

The development of a rational pharmacologic approach to dysfunction of the bladder outlet is difficult in part because of our lack of understanding of the physiology of continence and micturition. The gross anatomy of this region is itself controversial. The bladder is composed of a meshwork of smooth muscle bundles that interdigitate and are even seen to run at right angles to one another. In the area of the bladder outlet, these muscle bundles arch toward and away from the bladder neck in such a fashion that their contraction pulls open the bladder neck during micturition. Some of the inner layer of bladder smooth muscle may extend into the proximal urethra and, with contraction, produce the "funnel-shaped" opening of the proximal urethra seen at the initiation of voiding.24

Although no anatomic sphincter is present in the area of the bladder neck and proximal urethra, a physiological sphincter does exist. The mechanism(s) responsible for closure of the bladder neck and urethra is not understood. In fact, controversy exists as to whether continence is primarily a passive or an active event. An abundant amount of elastic tissue is present in this area and is probably largely responsible for determining the closure properties of this tissue. The tone of the bladder neck and urethral smooth muscle may also contribute to increasing outlet resistance. This smooth muscle is innervated by the autonomic nervous system and can be manipulated pharmacologically.

In addition to the proximal continence mechanism (bladder neck and proximal urethra), a distal continence mechanism also exists in the male. This mechanism (which is responsible for maintaining postprostatectomy continence)21 is situated in the distal prostatic urethra and membranous urethra, and has intrinsic and extrinsic components. The intrinsic component comprises those factors responsible for closure of the urethra itself (elastic fibers and smooth muscle tone). The extrinsic component is the striated muscle sphincter of the urogenital diaphragm. Although this striated muscle, which surrounds the urethra, is capable of interrupting the urinary stream and plays a role in the prevention of stress incontinence, it is not necessary for the maintenance of continence under normal circumstances.

The smooth muscle of the bladder neck and
urethra receives autonomic (sympathetic and para-
 sympathetic) innervation, whereas the striated
component of the distal continence mechanism re-
ceives somatic innervation. Although some investi-
gators have reported a “triple innervation” (para-
sympathetic, sympathetic, and somatic) to the
striated external sphincter,10 others have found no
evidence of an adrenergic innervation to this
muscle.23 It appears, therefore, that the use of
pharmacologic agents that act on the autonomic
nervous system (at least the peripheral autonomic
nervous system) is directed at modifying only
smooth muscle activity in the bladder and urethra.
Despite the fact that the importance of this auto-
nomically innervated smooth muscle in the pro-
cesses of continence and micturition is not pre-
cisely understood, pharmacologic manipulation
with autonomic drugs can be shown to alter blad-
der outlet resistance.

Organization of the Autonomic
Nervous System

The autonomic nervous system can be anatomi-
cally subdivided into the sympathetic and para-
sympathetic nervous systems. The sympathetic di-
vision is comprised of those nerve fibers that
originate in the thoracic and lumbar regions of
the spinal cord, whereas the parasympathetic cell
bodies are located in the cranial and sacral regions
of the cord. In general, both the sympathetic and
the parasympathetic nervous systems are com-
prised of preganglionic and postganglionic neurons
(Fig. 1). Preganglionic sympathetic nerves arise
from the spinal cord and synapse in ganglia located
near the spinal cord (paravertebral ganglia), be-
tween the paravertebral ganglia and end-organ
(preganglia), or near or within the end-organ (per-
ipheral ganglia). Sympathetic postganglionic fib-
ers then innervate the end-organ itself. Parasymp-
athetic preganglionic fibers usually synapse with
postganglionic neurons in ganglia near the end-
organ. In addition, sympathetic neurons synapse
with parasympathetic ganglia.24

It should be noted that the anatomic terms sym-
pathetic and parasympathetic are not synonymou-
with the physiological terms adrenergic and cholin-
ergic. Adrenergic and cholinergic nerves are de-
finied by the nature of their neurotransmitter. Cho-
linergic nerves are nerves whose neurotransmitter
is acetylcholine. These cholinergic nerves include
all somatic motor neurons, all preganglionic auto-
nomic fibers, and all postganglionic parasympa-
thetic fibers. The neurotransmitter released by ad-
renergic nerves is by definition a catecholamine.
Postganglionic sympathetic fibers are, in general,
adrenergic in nature, and the catecholamine re-
sponsible for neurotransmission in the lower urin-
ary tract is norepinephrine (Fig. 1).

Physiological Events at the Autonomic
Nerve Terminal

The complexity of events at the autonomic neu-
roeffector junction allows multiple sites for possi-
ble drug action.5,7 An adrenergic nerve terminal
is depicted in Fig. 2. Norepinephrine is synthesized
from tyrosine, the rate-limiting step being tyrosine

![Fig. 1 Organization of the autonomic nervous sys-
 tem.](image-url)