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Acetylcholine and the Overactive Bladder

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Currently, the most widely used and effective pharmacologic treatment for the overactive bladder (OAB) is administration of muscarinic receptor antagonists. This strongly suggests that acetylcholine plays some role in the aetiology of bladder overactivity.

If one considers the classical picture of the involvement of acetylcholine in the human bladder, this seems surprising. Acetylcholine is the main transmitter released from the parasympathetic nerves and is responsible for initiating synchronous contraction of the detrusor, resulting in the raised intravesical pressure that accompanies micturition.

Urodynamic studies of anaesthetised animals show the effects of antimuscarinic drugs that one might expect, that is, that inhibition of the muscarinic receptors leads to a progressive reduction in voiding efficiency, shown by a reduction of peak pressure, development of residual urine, and an increase in the frequency of micturition. Fig. 1 is from an experiment on anaesthetised guinea pigs carried out in my laboratory by Huw Williams (Derby) recording intravesical pressure and illustrating the effect of intravenous administration of atropine on the micturition cycle.

Micturition continued in the presence of atropine (albeit less efficiently) because in these small mammals adenosine triphosphate (ATP) is also a transmitter in the parasympathetic nerves and simultaneous inhibition of the appropriate purinergic receptors abolishes micturition completely. ATP appears to play little role in activating the human bladder, and antimuscarinic drugs would be expected to have the same effects as in animals, precisely what one would not want for the treatment of overactivity. In fact, use of antimuscarinics in OAB significantly reduces urgency, increases voided volume, and reduces frequency [1].

How can this be accounted for? This anomaly has led to an increase in the study of the underlying basis for bladder overactivity, the location of acetylcholine receptors, and the role of nonneural acetylcholine [2,3]. It has become apparent that the control of the bladder involves much more than the parasympathetic nerves. It is now clear that the urothelium is an active tissue that secretes chemicals that affect bladder activity and that we need to add to the equation another class of cell, the suburothelial interstitial cell, and consider the potential interactions between urothelium, sensory nerves, and interstitial cells.

The urothelium supports a trans-urothelial potential difference that is generated by ion transporting mechanisms [4], can be modulated by stretch and probably also by chemical agents in the urine, and is linked to secretion of chemicals. Initially nitric oxide (NO) and ATP were thought to be the main agents released from the urothelium, but more recently it has become apparent that the urothelium can also synthesise and secrete acetylcholine.

The paper by Lips et al. [5] unequivocally demonstrates the presence of acetylcholine in the human and mouse urothelium and examines the pathways to synthesis and release of nonneuronal acetylcholine in the bladder. The interesting conclusion is

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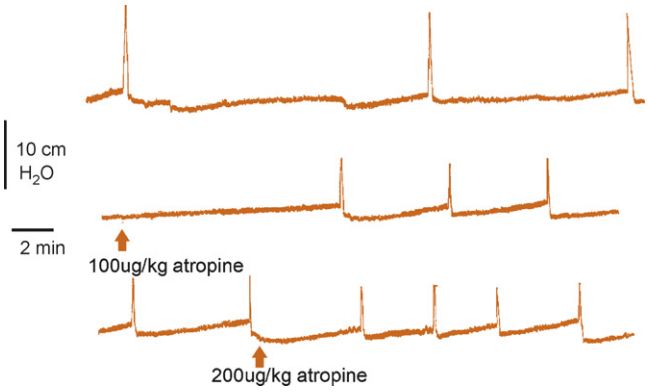

Fig. 1 – Urodynamic recording of the effect of intravenous atropine on intravesical pressure in a urethane-anaesthetised guinea pig.

reached that the molecular machinery used by the urothelium significantly differs from that used by the parasympathetic nerves for neuronal acetylcholine. The enzyme involved in urothelial acetylcholine synthesis was not choline acetyltransferase (ChAT) but carnitine acetyltransferase (CarAT), and the vesicular acetylcholine transporter (VAChT) responsible for transporting neuronal acetylcholine into vesicles was absent from the urothelium. The organic cation transporters (OCTs), which can mediate transport of acetylcholine in either direction across cell membranes, are, however, present in the urothelium.

These results are particularly interesting because they raise the possibility of developing drugs that can preferentially affect production and release of nonneuronal acetylcholine. The therapeutic value of any such selective drugs would depend on the function of nonneuronal acetylcholine. What role it plays, if any, in the physiology or pathophysiology of the bladder is, however, unknown. Below I will discuss some of the recent evidence about control of detrusor activity.

A new and probably important player is the interstitial cell. These are cells with characteristics similar to those of the interstitial cells of Cajal (ICCs) found in the gut. Several types of these cells are present in the bladder wall [6], and one type is present in the suburothelial layer, where interstitial cells form a two-dimensional network in close association with suburothelial sensory nerves and also with the urothelium. ICCs in the gut are involved in the generation and propagation of electrical slow waves that underlie the phasic spontaneous contractions characteristic of gut muscle. The function of interstitial cells has not been fully elucidated in the bladder, and although the bladder does generate spontaneous contractile activity, little evidence suggests that the interstitial cells are actual pacemakers, although they may be able to modulate the contractile activity. The interstitial cells respond to acetylcholine through muscarinic receptor stimulation (probably M3 receptors) by releasing intracellular calcium from a ryanodine-sensitive store (pers. comm., K. McCloskey, Queens, Belfast, Ireland).

Sensory nerves, as well as propagating impulses to the spinal cord, also send axon collaterals back to the bladder wall, where they may run in the suburothelial layer and release transmitters that interact with interstitial cells or the urothelium and also modulate intramural ganglia. Nerve terminals also express muscarinic receptors [7]. The parasympathetic nerve terminals, at least in the rabbit, seem to have functional excitatory M2 receptors increasing acetylcholine release and inhibitory M1 receptors reducing release. Whether or not the sensory nerve terminals have similar receptors is not clear, although currently evidence suggests they have [8].

There are thus many potential sites where nonneuronal acetylcholine could interact and have effects on the behaviour of the bladder. The urothelium itself also expresses acetylcholine receptors [9] and local paracrine release may be involved in feedback effects modifying its own function. These are areas where more research is badly needed to help us understand the interplay of mechanisms and allow more rational design of drugs to treat overactivity.

Another current treatment of overactivity, injection of botulinum toxin into the bladder, may be able to throw some light on the situation. This toxin works through blocking enzymes involved in vesicular release of transmitters. Although antimuscarinic agents and botulinum toxin will both reduce the effects of parasympathetic nerves on the bladder, in both cases, this need not be the essential mechanism for the relief of the symptoms. Botulinum toxin could also be reducing release of agents from sensory nerve terminals. However, if as Lips et al. [5] suggest, the nonneuronal acetylcholine release is not vesicular, then it is unlikely that the toxin will affect this source of acetylcholine, and this reduces the possibility that it is this acetylcholine and its effects that are being targeted for the symptomatic relief of overactivity.

As a pharmacologist who suffers from an OAB and has used antimuscarinic drugs for its relief, I will end with some personal comments. Despite the fact that antimuscarinics have been in shown in clinical trials to be statistically more effective than placebo, the effectiveness of the drugs as reported is actually pretty poor (for urgency episodes at a

baseline of about 5/d, after 12 wk of treatment, the placebo effect had reduced this to about 4/d, and effective doses of antimuscarinic drugs to about 3/d—still 3 too many) [1]. There is also in practice an extremely high dropout rate of those prescribed the drugs long term [10]. The two are clearly connected! It is well known to pharmacologists that cells adapt to the level of activation of their receptors. A reduction in receptor occupancy leads to enhanced sensitivity of the end organ to the transmitter. Thus, it is not surprising that the antimuscarinics lose their effectiveness. In my life antimuscarinics do play an important role. I do not take them continuously, but if I need an urgency-free period then antimuscarinics are extremely effective taken sporadically, far more so than any of the long-term clinical trials would indicate. A single dose of a short-acting drug will guaranteed me 4 h or more of complete protection, and the effect comes on within about 20 min. For all day protection, a slow-release preparation taken about 2 h beforehand will cover the day. However, the slow-release preparation only works effectively for about 10 d, after which the protection is minimal, and the symptoms transiently much worse when the drug is discontinued. I do not believe that antimuscarinics are the ideal drugs, and an increased understanding of the complex control of the bladder may lead to the development of drugs with better properties.

The elegant paper by Lips et al. [5] increases our understanding, but I will be surprised if nonneuronal acetylcholine does turn out to be the key—we are not there yet.

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