This Week's Citation Classic®

Paton W D M & Vizi E S. The inhibitory action of noradrenaline and adrenaline on acetylcholine output by guinea-pig ileum longitudinal muscle strip. *Brit. J. Pharmacol.* 35:10-28, 1969.
[Department of Pharmacology, University of Oxford, England]

Noradrenaline and adrenaline, but not isoprenaline or methoxamine, were found to inhibit the release of acetylcholine from Auerbach's plexus of the ileum. Alpha-receptor blocking drugs prevented this inhibitory action. Removal of sympathetic inhibitory tonic control by reserpinization or by alpha blocking drugs enhanced release of acetylcholine. The results provided neurochemical evidence for the existence presynaptically of alpha-receptors and for functional interaction between neurons. [The *SCI*® indicates that this paper has been cited in over 530 publications.]

"Cross Talk" Between Neurons

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I arrived from Hungary at the Department of Pharmacology in Oxford University as a postdoc with a Riker Fellowship in January 1967. I wanted to work with Sir William D.M. Paton. I still remember sitting in his office, which was overcrowded with books and old musical instruments, as we decided to study the possible presynaptic interaction between cholinergic and noradrenergic systems. The sympathetic outflow was at that time held to be antagonistic to the parasympathetic outflow at the effector cell level.

In his laboratory it was of course natural to use the stimulated ileum longitudinal muscle strip preparation with Auerbach's plexus attached, which offered a paradigm of the brain.[1] Although my country, Hungary, was then 10 years after the 1956 revolution, the regime did not allow me to bring my family, so I spent all my time in the laboratory. Never had my learning curve been so sharply exponential and sustained. For my personal scientific development, this paper, among all my publications, is the most important; since then I have been "married" to the study of modulation of chemical transmission.

We found that noradrenaline and adrenaline but not isoprenaline reduced both the resting and the stimulation-evoked release of acetylcholine from Auerbach's plexus. The inhibitory effect of noradrenaline was inversely related to the frequency of stimulation. Alpha-receptor blocking drugs (phentolamine, phenoxybenzamine) prevented the effect of catecholamines, indicating that alpha-receptors are also located presynaptically.

A puzzle was that other alpha-receptor agonists such as phenylephrine or methoxamine failed to inhibit evoked release of acetylcholine. But at that time the distinction between alpha-1 and alpha-2 adrenoceptors had not been made, and although we had all the evidence to suggest that presynaptically located alpha-receptors are different from those located postsynaptically, we failed to suggest a receptor difference.

The removal of noradrenergic innervation by reserpinization or receptor blockade enhanced the release of acetylcholine, indicating a local tonic control of cholinergic transmission by the sympathetic innervation. We suggested, therefore, that the "sympathetic control of acetylcholine release can be viewed as a kind of presynaptic inhibition, and when compared with an antagonism at the effector level, offers the physiological advantage of economy in transmitter release."

In retrospect it is interesting that the referee was skeptical of these findings, but the chief editor, W. Feldberg, found them interesting and accepted the paper for publication.

There are several possible reasons why this paper has been cited. First, the work gave the first neurochemical evidence for what is now known as a fundamental type of "cross talk" between neurons:[2,3] i.e., the release of a chemical substance from an axon terminal[4] that can inhibit the release of a transmitter from other adjacent varicosities with or without making synaptic contact.[2,3] Second, it was shown that alpha-receptors sensitive to noradrenaline but not to methoxamine were presynaptically located and that they mediate inhibitory action. Third, noradrenergic innervation of the gut was shown to exert a tonic inhibition on acetylcholine release from the enteric nerves. Fourth, the type of presynaptic action revealed laid the ground for later studies of physiological control by disinhibition and by negative feedback. Finally, the work prompted further studies, with M. Aboo Zar,[5] on the mechanism of acetylcholine release, leading to evidence for a role in transmitter release for (Na-K-Mg)-activated ATPase.

Several drugs in clinical practice are now available that have been developed to exploit the presynaptic modulation of neurochemical transmission. Although the neurochemical evidence for the presynaptic interaction between nerves is recent, the notion that the sympathetic nerves act on cholinergic neurons is a nineteenth century idea. In 1858 Joseph Lister, the famous surgeon, claimed that "the inhibitory influence does not operate directly on the muscular tissue, but on the nervous apparatus, by which its contractions are, under ordinary circumstances, elicited."[6]

1. **Paton W D M.** The action of morphine and related substances on contraction and on acetylcholine output of coaxially stimulated guinea-pig ileum. *Brit. J. Pharmacol. Chemother.* 12:119-27, 1957. (Cited 800 times.) [See also: **Paton W D M.** A "paradigm of the brain." Citation Classic. *Current Contents/Life Sciences* 32(45):16, 6 November 1989.]
2. **Vizi E S.** Presynaptic modulation of neurochemical transmission. *Prog. Neurobiol.* 12:181-290, 1979. (Cited 210 times.)
3. ———. *Non-synaptic interactions between neurons: modulation of neurochemical transmission.* London: Wiley, 1984. 260 p. (Cited 35 times.)
4. **Vizi E S & Knoll J.** The effects of sympathetic nerve stimulation and guanethidine on parasympathetic neuroeffector transmission: the inhibition of acetylcholine release. *J. Pharm. Pharmacol.* 23:918-25, 1971. (Cited 80 times.)
5. **Paton W D M, Vizi E S & Zar M A.** The mechanism of acetylcholine release from parasympathetic nerves. *J. Physiol.—London* 215:819-48, 1971. (Cited 230 times.)
6. **Lister J.** Preliminary account of an enquiry into the functions of the visceral nerves, with special reference to the "so called" inhibitory system. *Proc. Roy. Soc.* 9:367-80, 1858. (Cited 5 times since 1945.)

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