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This Week's Citation Classic®

Langer S Z. Presynaptic receptors and their role in the regulation of transmitter release. *Brit. J. Pharmacol.* 60:481-97, 1977.
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The paper discussed the presence of presynaptic receptors in noradrenergic nerve endings and their role in the regulation of the release of the neurotransmitter upon arrival of nerve impulses. [The *SCI*® indicates that this paper has been cited in over 970 publications.]

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This article corresponds to the Sixth Gaddum Memorial Lecture and represents a recognition of research contributions leading to the discovery of presynaptic autoreceptors, which are located on axon terminals and subserve the function of modulating the release of the neurotransmitter. The general view that transmitters can regulate their own release through an action on presynaptic inhibitory autoreceptors represents a new concept in the field of neurotransmission. While this article has been cited in over 970 publications, the first review on the same subject[1] and a more recent review[2] have also been extensively cited.

In 1969 I carried out the experimental work on the presynaptic modulation of noradrenergic neurotransmission in Buenos Aires as director of the recently created Instituto de Investigaciones Farmacológicas. During the two previous years, while working in Cambridge, England, I had analyzed the enhancement of noradrenaline release from the cat's nictitating membrane[3] by alpha-adrenoceptor blocking agents such as phenoxybenzamine. I returned to Buenos Aires with the thought that these alpha-adrenoceptors could be present on the nerve terminal. The experimental work carried out in Buenos Aires clearly suggested the existence of alpha-adrenoceptors on noradrenergic nerve terminals, which, when activated by the released neurotransmitter, lead to an inhibition of transmitter output. Since the adrenergic receptors were only known to be present in the postsynaptic effector cell, the existence of presynaptic alpha-adrenoceptors associated with the modulation of transmitter release represented a novel concept. In the scientific isolation of Buenos Aires, however, I was hesitant to submit any information for publication until we accumulated solid and convincing evidence as described in the first review.[1] In the political context of Argentina in the early and mid-1970s, buffeted between extreme left and extreme right, our institute seemed a haven of neutrality and scientific creativity.

Since initially postulated in the early 1970s, the concept that transmitters can regulate their own release through an action on presynaptic inhibitory autoreceptors has been well established for several neurotransmitters both in the peripheral and in the central nervous systems. In addition, this finding developed in parallel with the pharmacological evidence for the presence of two alpha-adrenoceptor subtypes, the α_1- and α_2-adrenoceptors, which are now well defined by different profiles of affinity and relative order of potencies for agonists and antagonists, as well as by different second messengers.

In addition to presynaptic autoreceptors, many nerve terminals possess presynaptic receptors sensitive to endogenous compounds other than the neuron's own transmitter. These presynaptic receptors are referred to as presynaptic heteroreceptors and are of considerable physiological and pharmacological interest because they are acted upon by cotransmitter neuropeptides, by transmitters released from adjacent terminals, or by locally produced or blood-borne substances that either facilitate or inhibit the release of different neurotransmitters.

More recently we reported[4] that a separate receptor-mediated process appears to modulate the presynaptic transporters for serotonin, norepinephrine, dopamine, and epinephrine. The modulation of the neuronal uptake of these monoamines involves a presynaptic site with many of the properties of a pharmacological receptor[4] that is different from the corresponding autoreceptor involved in modulating transmitter release.

This article is probably highly cited because it combines the historical background and the basic experimental evidence for the existence of presynaptic release-modulating receptors and discusses the physiological and pharmacological relevance of these receptors. I am particularly pleased that this article corresponds to the prestigious Gaddum Memorial Lecture.

As recently mentioned in another *Citation Classic* commentary on presynaptic receptors,[5] the hypothesis of presynaptic release-modulating autoreceptors was put forward independently by three other groups in addition to my own research team in Buenos Aires. The growing interest in presynaptic, release-modulating receptors includes the development of selective presynaptic receptor agonists or antagonists with potentially new and useful therapeutic properties.

1. **Langer S Z.** Presynaptic regulation of catecholamine release. *Biochem. Pharmacol.* 23:1793-800, 1974. (Cited 860 times.)
2. ————. Presynaptic regulation of the release of catecholamines. *Pharmacol. Rev.* 32:337-62, 1981. (Cited 530 times.)
3. ————. The metabolism of [^{3}H]-noradrenaline released by electrical stimulation from the isolated nictitating membrane of the cat and from the vas deferens of the rat. *J. Physiol.—London* 208:515-46, 1970. (Cited 185 times.)
4. ————. Presynaptic regulation of monoaminergic neurons. (Meltzer H Y, ed.) *Psychopharmacology, a third generation of progress*. New York: Raven Press, 1987. p. 151-7.
5. **Starke K.** Citation Classic. Commentary on *Rev. Physiol. Biochem. Pharmacol.* 77:1-124, 1977. (Cited 1,030 times.) *Current Contents/Life Sciences* 30(29):15, 20 July 1987.

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