This Week's Citation Classic®

Starke K. Regulation of noradrenaline release by presynaptic receptor systems.
Rev. Physiol. Biochem. Pharmacol. 77:1-124, 1977.
[Institute of Pharmacology, University of Essen, Federal Republic of Germany]

The review summarizes what was known 10 years ago about release-modulating receptors at noradrenergic axon terminals. Receptors for angiotensin, acetylcholine, prostaglandins, opioids, and adrenergic agents are discussed separately, followed by general problems such as the cellular mechanism of modulation and the general significance of presynaptic receptors. [The *SCI*® indicates that this paper has been cited in over 1,035 publications, making it the most-cited paper for this journal.]

Klaus Starke
Pharmakologisches Institut
Albert-Ludwigs-Universität
D-7800 Freiburg
Federal Republic of Germany

February 13, 1987

The 1950s and 1960s brought forth many scattered observations indicating that the axon terminals of a neurone are not merely sites from which the neuronal message is transmitted, but also sites at which messages are received; axon terminals increase or decrease the release of transmitter as required by chemical messages from the environment.

At the Department of Pharmacology at Essen, H.J. Schümann, U. Werner, and I studied the relationship between the renin-angiotensin system and the sympathetic nervous system. One finding was that angiotensin increased the release of noradrenaline from sympathetic axon terminals in the heart.[1] This interested me in the regulation of transmitter release in general, and I subsequently showed that noradrenaline itself and related drugs modified the release of transmitter noradrenaline. The axon terminals, it seemed, were sensitive to—or in other words, possessed receptors for—their own transmitter.[2] The same hypothesis was put forward independently by three other groups, that of S.Z. Langer in Buenos Aires, of S.M. Kirpekar in New York, and of L.O. Farnebo and B. Hamberger in Stockholm, making it a truly international idea. Moreover, presynaptic receptors of a neurone for its own transmitter were simultaneously postulated for cholinergic, dopaminergic, and serotonergic neurones. With these local autoregulatory mechanisms, the identification of axon terminals as transmissive *and* receptive structures came to a certain climax. In 1977 I tried to bring together all studies on the presynaptic regulation of noradrenaline release in the *Reviews of Physiology, Biochemistry and Pharmacology*, and Langer and T.C. Westfall did the same in other journals.[3,4]

What has made, and still makes, research on the presynaptic regulation of transmitter release so intensive? The answer is, I believe, that such research is relatively easy, broad, and promising. It is not too difficult to set up, for example, a brain slice, to stimulate the axon terminals by electrical pulses or high potassium concentrations, and to measure the efflux of neurotransmitter substances. Given the numerous transmitters, hormones, and tissue hormones now known, the study of presynaptic regulatory mechanisms is a vast field indeed. Finally, the results obtained may be highly relevant both physiologically and pharmacologically. For example, presynaptic receptors have become the prototypes of new receptor classes and have led to the current subdivision of α-adrenoceptors, serotonin receptors, and opioid receptors. For the pharmacologist, therapeutic implications are obvious.

Reviews probably tend to be quoted more often than original research papers. My article may have enjoyed frequent consultation because it comprehensively summarizes biochemical studies on the most thoroughly investigated neurone family, the family of noradrenergic neurones. It is also relatively simply constructed, addressing the same questions in turn to each presynaptic receptor. Finally, although it is limited to noradrenergic neurones, its arguments can be transferred to the variety of other neurone families. A review by me on one specific presynaptic receptor of noradrenergic neurons, the α-autoreceptor, has just appeared in the same journal that published the *Classic* paper.[5] *Habent sua fata libelli*—I wonder whether it will share some of its predecessor's popularity?

1. **Starke K, Werner U & Schümann H J.** Wirkung van Angiotensin auf Funktion und Noradrenalinabgabe isolierter Kaninchenherzen in Ruhe und bei Sympathicusreizung (Effect of angiotensin on function and norepinephrine absorption of isolated rabbit hearts at rest and during sympathetic stimulation). *Naunyn-Schmied. Arch. Pharmacol.* 265:170-86, 1969.
2. **Starke K.** Influence of extracellular noradrenaline on the stimulation-evoked secretion of noradrenaline from sympathetic nerves: evidence for an α-receptor-mediated feed-back inhibition of noradrenaline release. *Naunyn-Schmied. Arch. Pharmacol.* 275:11-23, 1972. (Cited 160 times.)
3. **Langer S Z.** Presynaptic receptors and their role in the regulation of transmitter release. *Brit. J. Pharmacol.* 60:481-97, 1977. (Cited 915 times.)
4. **Westfall T C.** Local regulation of adrenergic neurotransmission. *Physiol. Rev.* 57:659-728, 1977.
5. **Starke K.** Presynaptic α-autoreceptors. *Rev. Physiol. Biochem. Pharmacol.* 107:73-146, 1987.

CC/LS 1A15