Chemical Neurotransmission

75 years

Edited by

L. Stjärne P. Hedqvist

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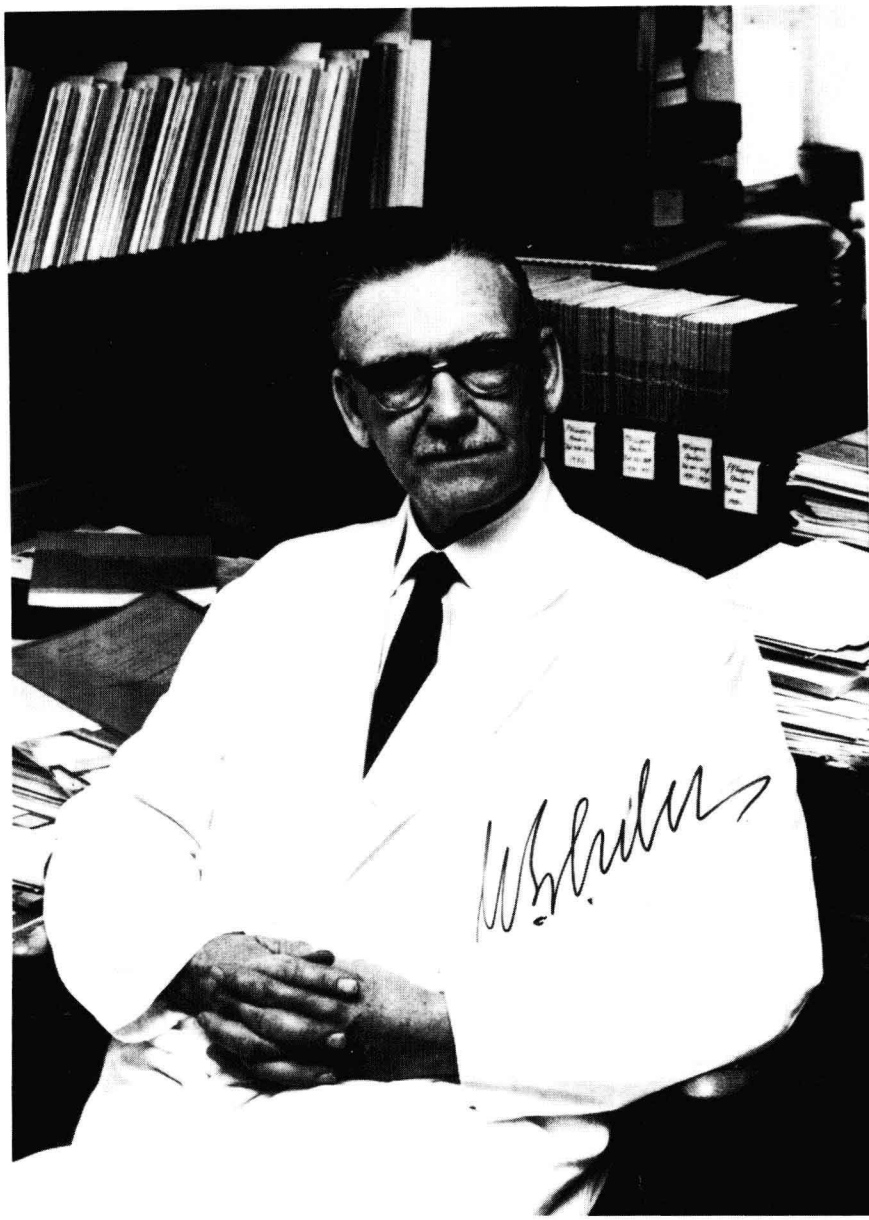
Dedicated to
Professor Ulf Svante von Euler



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(By courtesy N. O. Sjöstrand)

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Preface

Ulf Svante von Euler, who was to become one of the outstanding leaders of the field of 'Chemical Neurotransmission', was born on 7 February 1905. In the same year that field may be said to have received its birth certificate, in the full paper by T. R. Elliott, a British physiologist in his early twenties working in the prestigious laboratory of J. N. Langley in Cambridge (*J. Physiol., Lond.* **32**, 401–467). A facsimile of his preliminary report 'On the action of adrenalin', communicated by him to the Physiological Society in London on 21 May of the preceding year, is reprinted on pp. xvi–xvii in this volume.

On the basis of observations of the remarkable similarity between the effects of exogenous 'adrenalin' (a Parke-Davis preparation consisting, as later revealed, of a mixture of adrenaline and noradrenaline) and those of electrical stimulation of sympathetic nerves, in a number of tissues and species, Elliott prophetically proposed that 'adrenalin or its immediate precursor', somehow (he is rather vague on that point) liberated from a store 'in the neighbourhood of the myoneural junction', 'on each occasion when the impulse arrives at the periphery', may act as a chemical mediator of the nerve impulse to the effector organ.

Neither the concept that nerves may act on their target organs by secreting chemical signals, nor the capacity of 'adrenalin' to mimick effects of sympathetic nerve stimulation, were unknown at the time. The novel contribution of Elliott consisted in linking these elements, drawing the conclusion that therefore 'adrenalin' might be the mediator of nerve impulses in this particular class of neuroeffector junctions, and in verbalizing this to the scientific community. Thereby he transformed a possibly widely felt 'hunch' about neurotransmission into a scientific working hypothesis, explicit enough to be open to experimental verification or disproof. As a 'birth certificate' for Chemical Neurotransmission the publication of Elliott's hypothesis appears to be as worthy as any.

Oddly enough, with this flashing entry Elliott had already had his hour upon the stage of 'neurotransmitterology', and then was heard no more (in that field). Preserved testimonies from colleagues who knew him personally indicate that this daring contribution by a very junior scientist was received with remarkable indifference by the representatives of the Scientific Establishment of the day. Why? Was the time not ripe? Were the minds not prepared? Or are there other explanations?

Individual actors leave the stage, but the show—in this case the scientific race—goes on. Progress was remarkably slow, initially. Only after some

16–17 years were the crucial studies actually performed which tested the validity, in principle, of Elliott's idea. In 1921 in Vienna, Otto Loewi carried out a series of ingeniously conceived, but technically rather straightforward, experiments which provided direct proof for the chemical nature of neurotransmission both in parasympathetic and in sympathetic junctions, identifying (by a stroke of luck quite correctly, since he happened to work with frog heart) the transmitter in the latter with Elliott's 'adrenalin'.

This is where Ulf Svante von Euler entered the stage of 'neurotransmitterology', and of the study of biological information transfer by chemical signals in general. Son of a Nobel Laureate in chemistry (Hans von Euler-Chelpin, 1929), he was from the very beginning obsessed with a kind of cool determination to seek a chemical explanation for physiological (and pathophysiological) events. And he was abundantly successful. From the age of 26 he made, during the following 15 year period, three discoveries which have—although in two cases only after considerable dormancy—turned out to be of the most fundamental biological significance. In 1931, in work together with Gaddum, in Dale's laboratory in London, he found a novel biological principle which they named 'substance P'. Today this compound — possibly the first discovered peptide to turn out actually to function as a neurotransmitter in any sense—is strongly suspected of mediating transmission in, for example, primary pain afferent synapses in the spinal cord. Four years later he began work to characterize a biologically active principle in seminal fluid, the occurrence of which had been discovered by Kurzrok and Lieb a few years earlier. Von Euler patiently and skilfully continued the studies of its occurrence in the body, and of its biological and chemical properties, and named it 'prostaglandin'. More than anybody else he contributed to the inauguration of what is today known, as a result of the elegant analysis by Bergström and his coworkers, as the 'prostaglandin family', budding off during this last year the closely related 'leukotriene family', both including substances of the highest biological potency in many different directions, the physiological—and pathophysiological—significance of which is currently subject to intense study in many laboratories all over the world. And in 1946 von Euler made his third discovery, finally and conclusively verifying the validity in principle of Elliott's ambiguous, but weirdly accurate phrase that sympathetic neuroeffector transmission is chemically mediated, by 'adrenalin or its immediate precursor'. Von Euler showed that the mediator is, in most species, truly the immediate precursor of adrenaline, *N-O*hne-*R*adikal-(nor-)adrenaline. Ten years later, together with N.-Å. Hillarp, he prepared the first isolated fraction of noradrenaline-storing vesicles from sympathetic nerves, thus verifying the existence, and helping to disclose the nature, of Elliott's presumed neurotransmitter store 'in the neighbourhood of the

myoneural junction'. For these discoveries, on noradrenaline, von Euler was awarded the Nobel Prize for Physiology and Medicine in 1970, together with Julius Axelrod and Bernard Katz.

As former disciples of Ulf von Euler, and as humble workers in the vineyard of 'neurotransmitterology', we were taken by the idea of celebrating a double 75th anniversary in 1980: that of the man and that of the field. We are extremely pleased to have been granted the privilege of doing this in the form of The Second Nobel Conference of the Karolinska Institute, on 'Chemical Neurotransmission: 75 Years', in honour of Ulf von Euler. The meeting was held in Stockholm in December of 1980.

Our aim was not that of a parade, not a merely formal celebration. The field of Chemical Neurotransmission has grown so vast that we, along with many other workers, felt that a personal confrontation of the various specialists: electron microscopists, biochemists, electrophysiologists, neuropharmacologists, clinicians, etc., might be highly necessary in order to bridge the growing gap between those working in 'neurotransmitterology'. To our satisfaction some of the leading experts working on key aspects of the subject area accepted our invitation to participate in the conference, and to present their work in terms accessible to an audience of non-specialist neuroscientists. We think they succeeded in doing this in their original presentations, and we therefore hope that their contributions in this volume will be of interest not only to 'professional' neuroscientists, but also to graduate and advanced undergraduate students, clinicians, medical students and others who are curious about the most recent developments in our understanding of information transfer in the nervous system.

Our intention was not that the talks at the conference, or the papers in this volume, should cover all aspects of chemical neurotransmission, but rather highlight new developments. In addition to these contributions by invited speakers, the volume also contains the chairmen's overviews. In these the salient points from the discussions of the various sessions are presented, and the state of the art of the particular topic of each session outlined.

The editors are indebted to Drs T. Bartfai, B. B. Fredholm and A. D. Smith, who kindly assisted in building up the scientific programme of the Conference, and in preparing this volume.

Stockholm, June 1981

L. Stjärne
P. Hedqvist
H. Lagercrantz
Å. Wennmalm

PROCEEDINGS

OF THE

PHYSIOLOGICAL SOCIETY,

May 21, 1904.

On the action of adrenalin. By T. R. ELLIOTT.

(*Preliminary communication.*)

In further illustration of Langley's generalisation that the effect of adrenalin upon plain muscle is the same as the effect of exciting the sympathetic nerves supplying that particular tissue, it is found that the urethra of the cat is constricted alike by excitation of the hypogastric nerves and by the injection of adrenalin. The sacral visceral nerves, on the other hand, relax the urethra of the cat. But while the hypogastric nerves relax the tension of the bladder wall in the cat, they do not cause any similar change in the dog, monkey, or rabbit: and though, as is well known[1], adrenalin inhibits the cat's bladder, this reaction is the exception in the mammalian bladder, for adrenalin does not produce any change in those of the three animals named above.

I have repeated the experiment of clean excision of the suprarenal glands and find that the animal, when moribund, exhibits symptoms that are referable to a hindrance of the activities of those tissues especially that are innervated by the sympathetic. They lose their tone; and may even fail to respond to electrical stimulation of the sympathetic nerves. The blood-pressure falls progressively, and the heart-beat is greatly weakened. And at the latest stage previous to death, though the nerves of external sensation and those controlling the skeletal muscles are perfectly efficient, the sympathetic nerves exhibit a partial paralysis of such a nature that nicotine, when injected, is unable to effect through them a rise of blood-pressure or to cause dilatation of the pupil.

[1] Lewandowsky. *Centralblatt f. Physiol.* p. 433. 1900.

This marked functional relationship of the suprarenals to the sympathetic nervous system harmonises with the morphological evidence that their medulla and the sympathetic ganglia have a common parentage[1]. And the facts suggest that the sympathetic axons cannot excite the peripheral tissue except in the presence, and perhaps through the agency, of the adrenalin or its immediate precursor secreted by the sympathetic paraganglia.

Adrenalin does not excite sympathetic ganglia when applied to them directly, as does nicotine. Its effective action is localised at the periphery. The existence upon plain muscle of a peripheral nervous network, that degenerates only after section of both the constrictor and inhibitory nerves entering it, and not after section of either alone, has been described[2]. I find that even after such complete denervation, whether of three days' or ten months' duration, the plain muscle of the dilatator pupillæ will respond to adrenalin, and that with greater rapidity and longer persistence than does the iris whose nervous relations are uninjured[3].

Therefore it cannot be that adrenalin excites any structure derived from, and dependent for its persistence on, the peripheral neurone. But since adrenalin does not evoke any reaction from muscle that has at no time of its life been innervated by the sympathetic[4], the point at which the stimulus of the chemical excitant is received, and transformed into what may cause the change of tension of the muscle fibre, is perhaps a mechanism developed out of the muscle cell in response to its union with the synapsing sympathetic fibre, the function of which is to receive and transform the nervous impulse. Adrenalin might then be the chemical stimulant liberated on each occasion when the impulse arrives at the periphery.

[1] Kohn. *Arch. Mikr. Anat.* LXII. 1903.

[2] Fletcher. *Proc. Physiol. Soc.* This *Journal*, XXII. 1898.

[3] Cp. S. J. Meltzer and Clara Meltzer Auer, who obtained a like result after excising the superior cervical ganglion alone. *Amer. Journ. Physiol.* XI. 1904.

[4] Cp. Brodie and Dixon, this *Journal*, XXX. 1904, regarding its absence of action on the muscle of the bronchioles and of the pulmonary blood vessels; and also experiments quoted above on the bladder.