# THE INFLUENCE OF THE SYMPATHETIC NERVOUS SYSTEM AND SYMPATHOMIMETIC AGENTS ON VASCULAR SMOOTH MUSCLE

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SECTION I: STUDIES ON ISOLATED BLOOD VESSELS

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# INTRODUCTION

## *Historical Aspects*

Galen (circa A.D. 130-200) was probably the first to distinguish the sympathetic trunks. He regarded them as 'costal branches' of the 'sixth' pair of cerebral nerves (now known as the tenth pair, or vagi), and he realised that they descended across the roots of the ribs, received connections from the thoracic and lumbar parts of the spinal cord and were distributed to the viscera. He also described three swellings on each 'costal' nerve, one just above the level of the larynx, another at the thoracic inlet and a third in the upper abdomen. There is little doubt that these were the superior and inferior cervical (or stellate) sympathetic ganglia and the coeliac ganglia of the coeliac plexus. He suggested that the 'costal' nerves and their branches were the pathways through which the viscera were endowed with sensitivity and motor power.

Galen is said to have originated the idea that 'sympathy', or 'consent', exists between all parts of the body, and that the brain and nerves played an essential role in this relationship. He believed that the brain generated 'animal spirits' from the 'vital spirits' in the blood, and that the former were conveyed throughout the body by the 'hollow nerves' and their interconnections, so that every part was influenced and brought into 'sympathy'. Galen's ideas dominated all medical writing and teaching up to the middle of the 17th Century and it was not until that time that new information was added to the knowledge of the sympathetic nervous system.

Willis, in 1664, described, for the first time, the prevertebral sympathetic plexuses and their branches. He thought that the sympathetic trunks had an intracranial origin, but demonstrated the cervical ganglia and rami communicantes. He delineated more accurately the distribution of the thoracic splanchnic nerves. Willis adhered to the 'humoral theory', but differentiated 'voluntary' and 'involuntary' movements, ascribing to the cerebellum the special function of generating animal spirits which were responsible for involuntary activities such as the heart beat, respiration and gastrointestinal movements. The sympathetic ganglia he regarded as storage depots for animal spirits and considered that the rami communicantes strengthened, or reinforced, the sympathetic trunks, serving as channels through which involuntary spirits from the cerebellum and voluntary spirits from the cerebrum and cord could be brought together.

Winslow (1732) observed that interconnections existed between hepatic, renal and splenic plexuses. He was also the first to use the term 'great sympathetic' nerves to indicate their importance in effecting 'sympathy' between various organs.

Whytt's work (1751 and 1765) marked another conspicuous advance in knowledge of autonomic function. He adhered to the humoral theory in the main, accepting Willis's suggestions about the cerebellum and animal spirits, but he had a clearer understanding of the part played by the nervous system in the phenomena of 'sympathy'. He elaborated Willis's conception of voluntary and involuntary activities, and regarded reactions such as the contractions of the intestines and bladder as responses resulting from local stimulation produced by distension of the muscular walls or irritation of the mucosa. Whytt's theories provided the authentic basis of all modern ideas of reflex action.

About the middle of the 19th Century there was much conflict with regard to the nature and destination of the different types of fibres of the sympathetic nervous system. Some of the theories postulated were that: (a) the sympathetic fibres arose exclusively in the ganglia, but passed either peripherally along spinal nerves or centrally along spinal nerve roots; (b) the rami communicantes contained sympathetic fibres passing in both directions between the cord and the sympathetic ganglia; and (c) the rami communicantes contained sympathetic fibres arising only from the cord.

Remak (1854) showed that the white rami contained myelinated fibres, and traced them to the cord through both ventral and dorsal spinal nerve roots. He supposed that a proportion arose within the cord and he followed some of them through ganglia to terminations in higher or lower ganglia in the sympathetic trunk.

He also observed that the grey rami were composed of fine myelinated and unmyelinated nerve fibres which were distributed with the spinal nerves.

Gaskell (1886), from a series of anatomical studies, was able to demonstrate the cranial, thoraco-lumbar and sacral outflows of the autonomic nervous system, and he later grouped them together with the sympathetic trunks, and prevertebral and other ganglia as the 'involuntary nervous system'. Langley subsequently separated the nerves into the sympathetic and parasympathetic systems.

About the middle of the 19th Century striking advances in the understanding of the physiology of the autonomic nervous system were also made and its relationship to the adrenal medulla more clearly established.

One of the earliest clues as to the function of the adrenal medulla and to the action of the adrenal amines on the circulation was provided by the experiment of Brown-Sequard, in 1856, which showed that stimulation of the adrenal gland was followed by constriction of the cerebral vessels. In 1894, Oliver, a general practitioner in the Yorkshire town of Harrogate, who was interested in the problem of high blood pressure and the possible aetiological role of oversecretion of the adrenal glands, administered an extract of the adrenal gland to one of his children, and noted a decrease in size of the radial artery and a rise in blood pressure. The results of the experiment on his son impressed him so much that he travelled to University College, London, to discuss his findings with Professor E. A. Schafer. When he arrived in Professor Schafer's department, he found him engaged in an experiment in which the blood pressure of the dog was being recorded. When Schafer's experiment was finished, Oliver persuaded him to inject some of his suprarenal extract into the dog's vein. "They then stood amazed to see the mercury mounting in the manometer till the recording float was lifted almost out of the distal limb," (in Barcroft and Talbot, 1968). Oliver and Schafer together studied the nature of the adrenal extract in more detail over the next few years and showed, among other things, that the vasoactive principle of the adrenal gland was in the medulla and not in the cortex (Oliver and Schafer, 1895).

In parallel with these advances in knowledge of the physiological role of the adrenal medulla were the developments concerning sympathetic nerve function itself. Claude Bernard, in 1851 and 1852, showed that the division of the cervical sympathetic chain in the rabbit caused the ear of the same side to become flushed and warm. Stimulation of the sympathetic trunk had the reverse effects (Bernard, 1858). These observations indicated that the sympathetic nerves contained vasoconstrictor fibres and that under ordinary conditions the activity in these fibres kept the vessels in a partially constricted state.

The practice of cutting the sympathetic nerves to a part and thereby increasing its blood flow is one which is widely used today in surgical circles in the treatment of vascular insufficiency, particularly of the limbs. It owes its early beginnings to a chance observation made in 1923 on patients suffering from spastic paralysis who had been sympathectomised on the mistaken premise that it would alleviate this condition. It was found in this group that the limb on the 'treated' side felt warmer and appeared pinker than its fellow after the surgery (in Greenwood, 1967). Adson and Brown, at the Mayo Clinic, carried out lumbar sympathetic ganglionectomies on five spastic patients, beginning in May 1924, and carefully observed the changes in limb temperature, colour and sweat gland function. From this and subsequent work it became clear that following lumbar and thoracic sympathectomy there was warming of, and increased circulation through the feet and hands.

The possibility that the effects of stimulating the sympathetic nerve to an organ might be due to the liberation of a chemical substance from the nerve ending was suggested by the work of Lewandowsky in 1899. Elliott (1905) noted that the effects of adrenaline were almost identical with the effect of stimulating the sympathetic nerves to the part under study. However, despite the close similarity between the sympathetic transmitter and adrenaline in both chemical tests and biological action, there were certain differences to be observed in most situations. These differences were commented on by Barger and Dale (1910) who pointed out that the action of amino- and ethylamino-bases of the catechol group corresponded more closely with that of the sympathetic nerves than did that of adrenaline.

To explain these differences, Cannon and Rosenbleuth, in 1933, postulated the formation of two different substances, 'Sympathin E' and 'Sympathin I', at different end organs by the combination of released adrenaline with different substances in the cells.

Bacq, in 1934, suggested that the effects of sympathetic nerve stimulation were due to the liberation from the nerve endings of a substance which behaved like noradrenaline rather than adrenaline - really restating the suggestion of Barger and Dale made 24 years earlier - and this was supported by the observations of Stehle and Ellsworth (1937) and Melville (1937).

In 1939, Lissak made the first extractions from sympathetic nerves and showed that such extracts had an adrenaline-like action. However, he was not able to define the precise nature of these extracted substances. In 1946, U. S. von Euler and his colleagues in Stockholm devised more refined methods for purification and biological and chemical analysis of catecholamines, and found that they could extract from the hearts of cattle, horses and cats a substance identical with noradrenaline in all its characteristics.

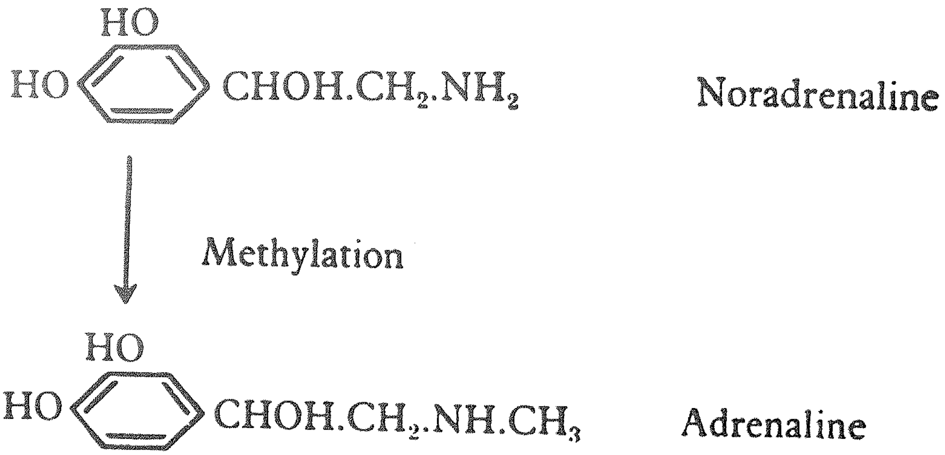

Fig. Intro. 1 - The structures of adrenaline and noradrenaline.

In 1947, Gaddum and Goodwin carried out experiments on the cat, in which they observed the blood pressure, pupil reactions and uterine contractions, and gave adrenaline and noradrenaline intravenously and compared their effects with those of stimulation of the hepatic nerves. They concluded that the substance released by the hepatic nerves was not adrenaline but noradrenaline or tyramine. Noradrenaline differs from adrenaline in its structure only in the absence of a methyl group (Fig. 1), but this difference confers quite different properties on the two substances.

The pharmacological actions of these substances on the cardiovascular system are still being elucidated, but an important step in this direction was provided in 1948, when Raymond Ahlquist hypothesised that there were two types of adrenotropic receptors on vascular smooth muscle, as determined by their relative responsiveness to the series of racemic sympathomimetic amines most closely related structurally to adrenaline. The α-receptors, he postulated, were associated with most of the excitatory functions (viz., vasoconstriction, stimulation of the uterus, nictitating membrane, ureter and dilator pupillae) and one important inhibitory function, intestinal relaxation. The β-adrenotropic receptor was associated with inhibitory functions (i.e., vasodilatation, relaxation of uterine and bronchial musculature) and one excitatory function (myocardial stimulation). The results of Ahlquist's experiments suggested that there was only one adrenergic neurotransmitter, and its combination with one or other of the two receptors mentioned in the foregoing produced either an excitatory or an inhibitory effect.

In 1962, Cooper, Jellinek, Willman and Hanlon extracted noradrenaline from human heart biopsy specimens, while in 1963, Chidsey, Braunwald, Morrow and Mason found that the noradrenaline content of biopsy specimens of human heart was reduced by treatment with reserpine. It was inferred that the noradrenaline found in these tissues was derived from neurotransmitter stores.

The introduction of a fluorescent histochemical technique by which noradrenaline and adrenaline could be separately identified in tissues has helped in characterising further the presence and nature of the sympathetic transmitter. This technique was introduced by Falck in 1962, and in 1963, he and Rorsman studied punch-biopsy specimens of human skin using the method, and were able to demonstrate catecholamines at the outer border of arterial smooth muscle. Up to this time, this was probably the only direct evidence there was of the presence of these substances in arterial smooth muscle in man. In 1967, however, Waterson, using a modification of the Falck technique, was able to demonstrate noradrenaline in a proportion of blood vessels of fresh human dental pulp (Waterson, 1967) which was later confirmed by Kukletova, Zahradka and Lukas (1968).

The characterisation of the sympathetic neurotransmitter in man and the mechanism of its release from sympathetic nerve endings is both of physiological and pharmacological significance, as a large number of therapeutic agents owe their action to interference with the synthesis, storage, release, re-uptake and inactivation of this substance. The sympathetic nervous system plays an important part in man's cardiovascular homeostasis, whether it be in response to a thermoregulatory stimulus, the need to main a constant blood pressure, or to meet the body's metabolic requirements. Using newer techniques, such as fluorescence histochemistry, electron microscopy and more refined assay methods, the nature of the sympathetic transmitter and its physiological role is now more apparent. However, there are certain areas in the human circulatory system, as, for example, the peripheral circulation, where the distribution of sympathetic nerves to the blood vessels, and the action of sympathomimetic substances and ions on these structures needs further elucidation. The material presented in this thesis examines some of these aspects of the human peripheral circulation.