Physiology Past, Present & Future

A symposium in honour of Yngve Zotterman

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Physiology
Past, Present and Future

Yngve Zotterman and his friends
Bristol, July 1979

Left to right: Alex von Muralt, Richard Adrian, Lloyd Beidler, Carl Pfaffmann, Yngve Zotterman, Manfred Zimmermann, George Gordon, Sven Landgren, Herbert Hensel, Dan Kenshalo, Ainsley Iggo.

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PREFACE

The idea for this Symposium was conceived following the Satellite Symposium entitled "Pain in the Trigeminal Region" in Bristol in 1977, after the I.U.P.S. Congress in Paris. As President of I.U.P.S. and Chairman of the I.U.P.S. Commission on Oral Physiology, Yngve Zotterman swept aside many of the early difficulties which faced us in organising that symposium and during the meeting he showed a breadth of knowledge and intellectual liveliness of which many people half a century his junior would be proud.

When I learned - to my surprise - that Yngve was to reach the age of 80 in September 1978, and recalling his enjoyment of the Bristol Symposium in 1977, I thought that he would welcome another meeting in Bristol to celebrate his great age and achievement, in the company of some of his distinguished friends and collaborators. It was neither possible nor desirable to have the meeting at the time of his 80th birthday when he was to be with his family and very close friends in Stockholm, so July 1979 was chosen, when we dared to hope that the weather might allow us to enjoy the occasion to the full. Not only was the weather kind to us, but so also were his friends who came to do him honour, the many organizations which provided financial and other material support, and my own colleagues who, in many large and small ways, made my task easy and the occasion successful.

It is hard to credit that Yngve Zotterman entered the Karolinska Medical School over 60 years ago in 1916 and that he joined an advanced class in physiology in Langley's laboratory at Cambridge in 1919 where he was taught by Joseph Barcroft, A.V. Hill, H. Hartridge and of course, E.D. Adrian, with whom he returned to work in 1920 and again in 1925. Yngve's first paper presented at the Physiological Society and published in the Proceedings in 1920, was entitled "The conductivity of the nerve ending in acid solutions". Five years later he went back to Cambridge and in 1926 with Adrian published two papers entitled "The impulses produced by sensory nerve endings" (Parts 2 and 3) on which his reputation as a neurophysiologist was to be built. It is perhaps not so well known that during this period in England he worked for a while with Sir Thomas Lewis and with Lewis published two papers on the vascular reactions of the skin. Towards the end of 1926 he joined A.V. Hill in experiments on heat production of nerve. His research has also ranged over heavy work in lumber-men and deep water diving and for many years since 1935 he has studied the neural mechanisms of taste. It was Yngve who made the first recordings in conscious human subjects of subjective sensations in response to gustatory stimuli, relating them to the nerve impulse pattern in the chorda tympani.

Yngve's energy seems limitless and the list of distinguished organizations on which he has served is too long for me to include. For five years from 1967-1972 he was President of the Trustees of the Nobel Foundation and from 1971-1974 he was President of the I.U.P.S. He is secretary of the Wenner Gren Centre in Stockholm and still organizes symposia at the Centre. In 1973 he founded the "Working group for the study of the problems of elderly people" and has edited 7 volumes of symposia already. I know that there are more to come.

Yngve has received many tributes at home and abroad to his academic achievements, none I suspect more proudly accepted than the Sc.D. at the University of Cambridge in 1968, conferred on him by his old friend E.D. Adrian, who was Chancellor of the University at the time.

This is the man in whose honour we foregathered in Bristol in July 1979. Those of us who were there are glad to know that Yngve greatly enjoyed the occasion, as we did also.

Declan Anderson

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The University of Bristol kindly provided hospitality.

INTRODUCTION

I find myself writing this introduction for what one might call family reasons. But birthdays are occasions when family feelings are important and I was indeed delighted to have been asked to be at the meeting which this volume commemorates. I was there as a naive observer to learn about new work in a field which I think I might be said to have grown up with - at any rate I grew up in a world bestrode by neurophysiological collosi of whom Yngve was one. I hardly thought when I first met Yngve that I should have the opportunity and pleasure of hearing him talk on the future of Physiology, with all his experience and the wisdom of 81 years. To be honest, I think I was hardly thinking of physiology at all - I daresay I wasn't even thinking.

Our first encounter, I'm told, was more than 50 years ago, so I can, I think, claim a lifelong friendship as an excuse for having been at the meeting. Over the years, my childhood affection has matured into scientific admiration. It was great fun to congratulate Yngve in his eighty-first year. We listened, as I think my father would have said, to lots of really exciting stuff and I know how very much pleasure it would have given him to have been at the meeting to add his congratulations to the birthday celebrations. Yngve was in at the very beginning of sensory electrophysiology and his contributions form part of what every biologist knows. Indeed, they know it almost before they are taught it, so much has it become part of general knowledge. He has continued over his entire life to be amongst those who with their own hands have added to scientific knowledge and I should like to make a prediction about the future, and that is that in the field of sensory neurophysiology, Yngve's fundamental work will continue for years to inform and inspire both our experimental work and our ideas.

Richard Adrian

CONTENTS

THE SAGA OF THE 'C' FIBRES

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ABSTRACT

The non-myelinated axons in peripheral nerves were originally reported in 1838 by Remak , although their detailed description had to await the introduction of the electron microscope. Most of them are dorsal root afferent, but some enter the spinal cord via the ventral roots. Their functional characteristics, and particularly the rôle in pain attracted attention in the 1930's. The introduction in 1956 of single unit C-fibre recording yielded exact information needed for a satisfactory analysis of the receptor characteristics. A broad survey is made of C-fibre afferents in the viscera, skin and deeper somatic tissues. The action of these C-fibres in the central nervous system, principally in the dorsal horn of the spinal cord is briefly reviewed.

KEYWORDS

Afferent C-fibres, non-myelinated axons, cutaneous receptors, visceral receptors, muscle receptors.

INTRODUCTION

The existence in peripheral nerves of very small axons was first demonstrated by Remak in 1838, who microdissected peripheral nerves in water. He saw very fine interlacing filaments with nucleated corpuscles, subsequently found to be Schwann cell nuclei (Fig. 1A). These filaments have become known as Remak bundles or Remak fibres. Tuckett (1895) using a technique of teasing the nerve apart in aqueous humour, was able to distinguish three components in Remak's fibres - nuclei of the sheath (Schwann) cells, a sheath and the cores of the fibres (Fig. 1B). The C, or more correctly, the non-myelinated (non-medullated, unmyelinated) fibres in peripheral nerve thus have a long scientific history. They were revealed with improved clarity in Ranson's modification of Cajal's silver stain for axons. He found them to arise principally from dorsal root ganglion cells (Ranson, 1911) and to be segregated in the lateral division of the spinal dorsal roots in cats and to enter the dorsal horn immediately, or after a short passage in Lissauer's tract. This separation is clearly marked in primates. It gave an opportunity to assess experimentally their sensory rôle. When this lateral division of the dorsal root was sectioned by Ranson in cats, the 'pseudo-affective reflexes' were found to be weaker in response to previously effective noxious stimuli. Although the dorsal

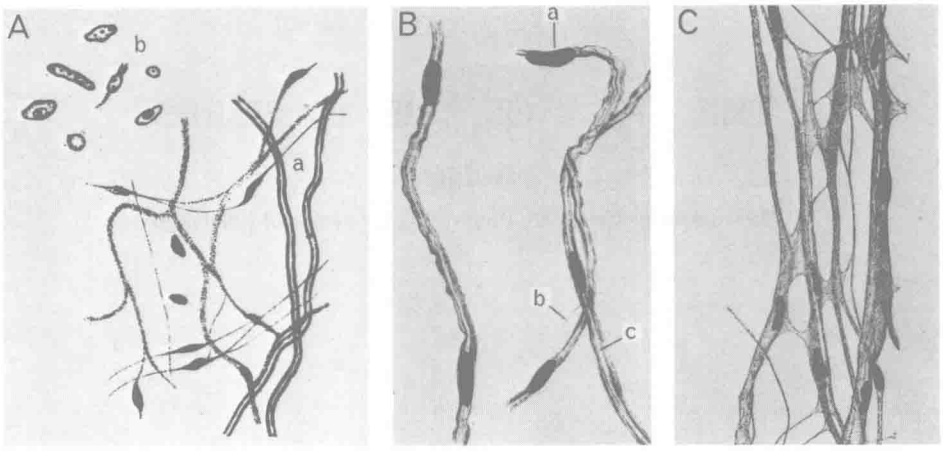

Fig. 1. Diagrams to illustrate successive stages in the recognition of C-fibres in peripheral nerves. A. Remak's original (1838) drawing of nerve fibres dissected in water. The thick large fibres (a) are myelinated axons with an axis cylinder and the interlacing filaments (fibrae organicae) are the Remak bundles of C-fibres. The corpuscular bodies (b) are what we now call Schwann cell nuclei. B. Tuckett's (1895) drawings of Remak's fibres, showing (a) the nuclei of the sheath cells (b) sheath and (c) cores of the fibres, equivalent to axis cylinders. C. Nageotte's (1922) figure of cat cervical sympathetic C-fibres, showing clearly the anastomosing system. Only the satellite (sheath) cells branch, the axons are continuous unbranched individuals.

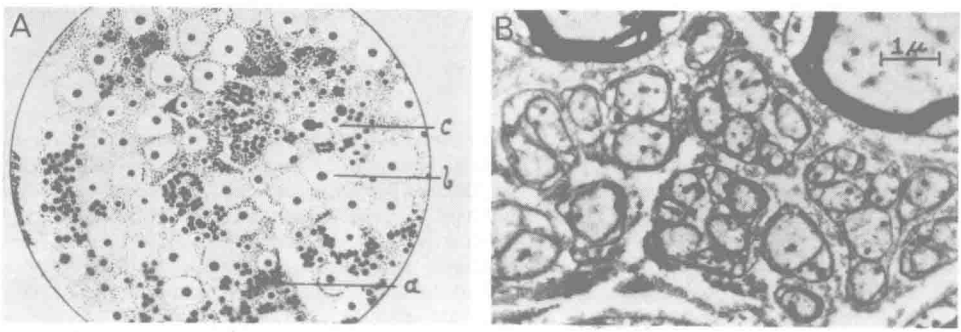

Fig. 2. Histological advances. A. Ranson's (1911) original illustrations of pyridine silver stained peripheral nerve, showing a) non-myelinated fibres, b) large myelinated fibres and c) small myelinated fibres. B. Gasser's (1955) electron micrograph of nerve showing a myelinated axon and several bundles (Remak's fibres) of non-myelinated axons.

root afferents that run into Lissauer's tract include both small myelinated and non-myelinated axons, the idea was established that the small fibres, including C-fibres, were pain fibres. There are also, of course, numerous C-fibres which are part of the autonomic nervous system.

This classical Bell-Magendie view of the afferent fibres has been modified by the work of Coggeshall and Willis and their colleagues on the spinal ventral roots. These roots have long been known to contain C-fibres and also neuronal cell bodies. Coggeshall, Coulter and Willis (1974) have now established that many ventral root C-fibres are afferent. The C-fibres comprise about thirty per cent of the ventral root fibres and about half of them are sensory. There are therefore substantial numbers of afferent C-fibres that enter the small cord through the ventral roots. Only a very small number of myelinated afferent fibres take the same course (Applebaum and others, 1976). Clifton and others (1976) dealing with the sacral and caudal roots of the cat report that the afferents are distributed widely among the pelvic viscera as well as to the skin and deeper somatic structures. In general they had relatively insensitive receptors. Those in the viscera were either mucosal, responding to severe mechanical stimuli, or were distension sensitive. The new results present a challenge to the classical Bell-Magendie Law but little is yet known of the sensory or reflex functions of the ventral root afferent C-fibres. They could be nociceptors.

ELECTROPHYSIOLOGY. WAVES AND UNIT POTENTIALS

The introduction in 1924-6 by Adrian (1926) of techniques for electrical recording of sensory impulses from nerve endings and particularly the results obtained by Adrian and Zotterman (1926) using a single end organ preparation both heralded a new epoch in neurophysiology and gave promise that the C-fibres would soon reveal their secrets. Not so. In 1931 in his Croonian lecture Adrian was able to surmise that something must be going on in the small fibres, but the capillary electrometer was too insensitive to reveal what it was. In fact, when we consider the kind of evidence provided by the capillary electrometer used in the original studies and Matthews' oscillograph used for the later studies (Fig. 3), and the constraints they imposed on the investigators, we can only admire the success achieved.

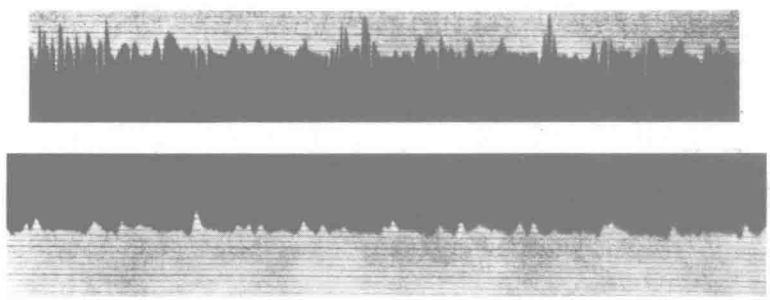

Fig. 3. Records obtained using the Matthews' oscillograph of action potentials recorded by Zotterman (1933) from dorsal cutaneous nerves of the Frog. Upper record, response to pin thrust into the skin at start of tracing. Lower record, response to radiant heat applied to the skin, causing slow action potentials to appear in the record.

Now enters the C-wave of the compound action potential which has given its name to the laboratory jargon for the non-medullated axons in peripheral nerves. Gasser and Erlanger introduced and developed the application of the cathode-ray oscilloscope and thermionic amplifiers to the point where, in excised peripheral nerves, it was possible to detect, first a synchronous volley of impulses in the largest and fastest myelinated axons (the A wave), then the slower B wave and finally after some doubts and refinement of the techniques, the C-wave (Erlanger and Gasser, 1930). The correlation of these waves with the various sizes of axon in peripheral nerve occupied Erlanger, Gasser and Bishop for several years but the main picture was clear by the time of the publication of Erlanger and Gasser's monograph in 1937, and the C-wave was established as originating in the non-myelinated axons. In 1955 Gasser returned to the C-fibres and showed in the sural nerve of the cat that they conduct at velocities between 2.3 and 0.6 m/s, thus amending the original conduction rates "of the C-fibres 1.6 - 0.3 m.p.s" (Erlanger and Gasser, 1930).

Meantime, the search for the axons of receptors with high sensitivity to noxious stimuli continued in Europe using the technique of unit recording. An active laboratory in this search was that of our Guest of Honour, Yngve Zotterman. He followed up the advances that flowed from the introduction of Matthews' sensitive amplifying and recording system that replaced the capillary electrometer. Even with this new device Adrian, Cattell and Hoagland in 1931 were unable to subdue the C-fibres. Meantime, the existence of large and small afferent fibres and their relative sensitivity to conduction block by ischaemia, cold, local anaesthetic and/or pressure had led Zotterman (1933) to give strong support to the view that first and second (burning pain) were due to impulses in myelinated and non-myelinated fibres respectively and thus to promote the view that the C-fibres were pain fibres. Attempts to separate the different waves of the compound action potential in peripheral nerve established that the C-wave was more readily blocked by local anaesthetic and less sensitive to ischaemia than the largest components of the A-wave. This gave promise of an attribution of sensory functions to the C-fibres in peripheral nerves. The A-fibres were already regarded as necessary for tactile sensory inputs. Clarke, Hughes and Gasser in 1935 showed that the C-fibres mediated pain but that the localized cutaneous pain was mediated by small myelinated axones. In man, knowledge about differential block in peripheral nerve of A and C-fibres, as well as the existence of first and second 'pain' led to the attribution

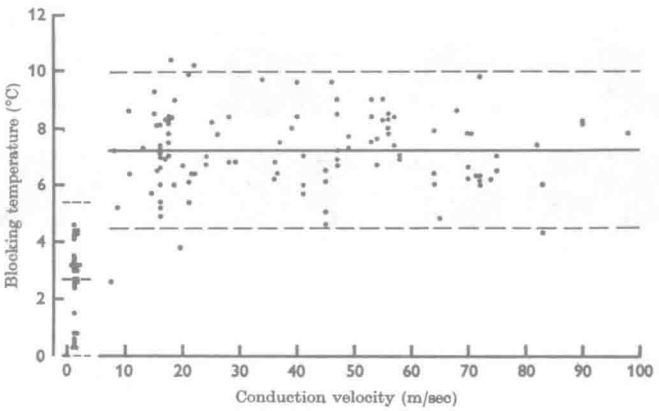

Fig. 4. Relation between conduction velocity of axons in the saphenous nerve and the temperature at which conduction is blocked. ● - myelinated axons, O - non-myelinated axons. The mean blocking temperatures were 7.2°C for the A-fibres and 2.7°C for the C-fibres (from Franz and Iggo, 1968).

of second pain to C-fibres by Zotterman in 1933. Even here the claims were contested, and recent single unit studies have shown that differential block by cold (Paintal, 1965; Franz and Iggo, 1968), local anaesthetic (Franz and Perry, 1974) and probably by ischaemia is less selective than once thought. Although A and C-fibres can be separated by selective block (Fig. 4) the various A-fibres cannot, particularly when natural repetitive stimulation via receptors is used as the input. This is due to the frequency-related Wedensky inhibitory actions (Paintal, 1965). This can even prevent a separation of A and C-fibres. Although the C-fibres can still conduct at temperatures below the absolute blocking temperature for A-fibres (Franz and Iggo, 1968) they may nevertheless block at higher temperatures, if the firing rate in the C-fibres is high.

The story continues, with an analysis by Zotterman (1936, 1939) of the effect of recording conditions, and particularly of the axon diameter and the correlated inter-electrode resistance on the signal:noise ratio and the spike amplitude of individual axons in unit recording. As a result he was able to secure from fine fascicles of peripheral nerves, records of the impulses in small mammalian axons. These were published in the Journal of Physiology in 1939 and the records clearly show very small waves of relatively long-time course that could be evoked by tactile and by noxious stimulation of the skin (Fig. 5). Because of the simultaneous presence in the records of larger action potentials and the uncertain number of axons generating the small waves, it was a matter of fine judgement to decide whether a particular fibre had a unique receptor characteristic. The small waves

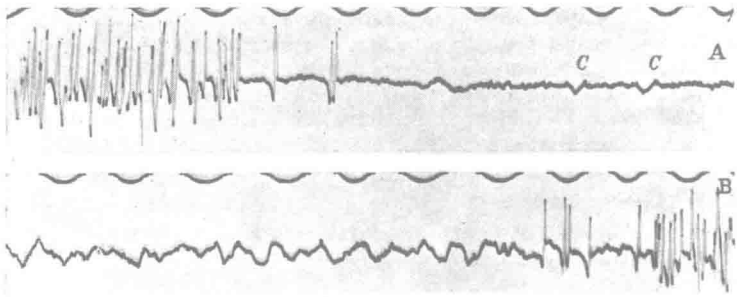

Fig. 5. Action potentials from a small fascicle of the saphenous nerve of a cat, in response to firmly stroking the skin, twice a second. The records read from right to left. In A, the start of the stroke was towards the left, setting up large impulses and B, shows the end of the stroke, which was followed by an after-discharge of small irregular waves. Individual small waves, labelled C, are present at the beginning of the upper record. These are residual after-discharges following a previous stroke. The fine marks are 50/s (Zotterman, 1939).

appeared in response to various natural stimuli, but in particular they could be evoked by holding a naked flame close to, or on, the skin. Here then were the long sought mammalian afferent units fitted to the task of signalling 'pain'. Their assignment to C-fibres by Zotterman was based on their spike-amplitudes using his analysis of the influence of recording conditions on spike size. The small size of the impulses, however, prevented conduction velocity measurement and Zotterman concludes that "As direct data of the velocity of these very small spikes is still lacking, it is possible that the potentials here recorded travel at lower rates than is indicated by their spike heights". (Zotterman, 1939).