Recent Advances in the Pharmacology of Adrenoceptors

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Elsevier/North-Holland

RECENT ADVANCES IN THE PHARMACOLOGY OF ADRENOCEPTORS

Proceedings of a Satellite Symposium of the 7th International Congress of Pharmacology held at Owens Park, Manchester, on 24th-26th July, 1978.

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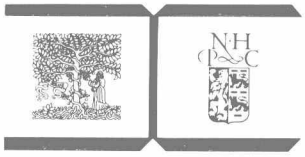

1978

ELSEVIER/NORTH-HOLLAND BIOMEDICAL PRESS
AMSTERDAM-NEW YORK-OXFORD

ISBN Elsevier/North-Holland: 0-444-80083-2

Published by:
Elsevier/North-Holland Biomedical Press
335 Jan van Galenstraat, PO Box 211
Amsterdam, The Netherlands

Sole distributors for the USA and Canada:
Elsevier North-Holland Inc.
52 Vanderbilt Avenue
New York, N.Y. 10017

Printed in the Netherlands

FOREWORD

Dale was the first to propose that the hormone adrenaline acted at specific sites in the vascular bed: its action at some of these sites caused contraction, and at other sites relaxation of the smooth muscle of the arterial wall. This functional classification of adrenoceptors into excitatory and inhibitory receptors was later complemented by a pharmacological classification proposed by Ahlquist in 1948. Ahlquist distinguished between α- and β-adrenoceptors on the basis of the rank order of potency of different adrenergic agonists. The idea of two pharmacologically distinct adrenoceptors gave rise to the synthesis of specific antagonists acting at either of these receptors, followed by a great volume of pharmacological work resulting in comprehensive adrenoceptor 'maps' for different tissues in different species.

The last few years have seen an explosion of information on adrenoceptors. Direct receptor labelling techniques have enabled investigators to attach radioactive labels to adrenoceptors, thus further confirming Ahlquist's classification. It became obvious that adrenoceptors, as detected with radioligand labelling, are much more wide-spread than previously suspected: apart from smooth muscle and gland cells, these receptors can be found also on fat cells, blood cells, glia cells, and nerve cells. Further information has accumulated about the biochemical changes which may follow the activation of adrenoceptors, and the possible role of cyclic nucleotides as second messengers has become much clearer. It has been also possible to dissect the 'recognition site' of the receptor from the 'amplification site', and for the first time, it has become possible to reconstruct the sequence of events between the binding of the agonist to the receptor site and the elicitation of a series of sub-effects resulting in the final effect. The concept of 'release-modulating' or 'presynaptic' adrenoceptors has been further developed, and the pharmacological characteristics of these receptors have been established (cf. α_1 vs. α_2 adrenoceptors). Developments with electrophysiological techniques have enabled investigators to study membrane responses to catecholamines, and to correlate these with receptor mechanisms. In smooth muscle and gland cells, both intracellular recording and the sucrose gap technique have been used and the ionic mechanisms underlying the membrane responses have been studied. In the central nervous system, the technique of microelectrophoresis has revealed the existence of both α- and β-adrenoceptors. Recent developments in biochemical, physiological and pharmacological techniques have enabled investigators to study the plasticity of adrenoceptors: the effects of temperature, ageing and hormones

on receptor numbers and pharmacological responsiveness in different tissues have been investigated. Finally, a lot of information has been accumulated about the role of adrenoceptors in human disease (e.g. essential hypertension, bronchial asthma, glaucoma, and migraine).

It seemed, therefore, to be important to have a meeting for people working with different aspects of adrenoceptor pharmacology in order to try to correlate findings obtained with different techniques, and to come to a mutual understanding concerning concepts and terminology. The Summer of 1978 was an opportune time for such a meeting since many pharmacologists from all parts of the world attended the 7th International Congress of Pharmacology in Paris.

The Adrenoceptor Symposium in Manchester followed the Paris Congress. The meeting lasted for three days and consisted of six Sessions. Each Session was introduced by a Chairman, and was summed-up by a Discussant. 31 contributed papers were presented in the form of poster demonstrations. The Proceedings of this meeting are presented in this book.

Such a meeting would not have been possible without the help and hard work of many devoted people. We are grateful for the help of H. Schnieden, E.S. Johnson, and B.L. Ginsborg who worked with us on the Programme Committee. We wish to thank the University of Manchester for excellent conference facilities, and the City of Manchester for a Civic Reception. We are indebted to our many sponsors for the generous financial help which enabled us to organize this meeting; the names of our financial sponsors are listed on a separate page. We wish to thank P. Brown of Elsevier/North Holland for his efforts in bringing this book together. Last, but not least, we are grateful for the excellent secreterial help of Hilary Neve and Pamela Bluhm.

Manchester, July 1978

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ACKNOWLEDGEMENTS

The financial help of the following is gratefully acknowledged:

Abbott Laboratories Limited
Allen & Hanburys Limited
Beecham Pharmaceuticals
Berk Pharmaceuticals Limited
CIBA Laboratories
Elsevier/North Holland Biomedical Press B.V.
Geigy Pharmaceuticals
Imperial Chemical Industries Limited
Janssen Pharmaceutical Limited
Lepetit Pharmaceuticals Limited
Lilly Research Centre Limited
Lundbeck Limited
May & Baker Limited
Merck Sharp & Dohme Limited
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William R. Warner Limited
Wellcome Trust
Wyeth Laboratories

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ELECTROPHYSIOLOGICAL CONSEQUENCES OF ADRENOCEPTOR ACTIVATION: SMOOTH MUSCLE, LIVER AND GLAND CELLS

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The cells of the liver, the exocrine glands and the smooth muscle of visceral organs and blood vessels obviously subserve quite different physiological functions. They have in common a degree of innervation from noradrenergic neurones and the likelihood of exposure to adrenaline released from the adrenal medulla.

In discussing these cells we are faced with the diversity of response to excitation: mechanical change for smooth muscle, metabolic transformation for the liver and secretion for exocrine gland cells. Yet they have turned out to have much in common electrophysiologically and ionically. We shall see that the discussion of electrophysiological activity quickly becomes a discussion of ionic movements and that we are never far from the fundamental involvement of calcium ions.

Usually, questions about the basic electrical excitability of these cells and the ionic events underlying them have been asked in advance of questions about the modes of action of catecholamines. This was the approach pioneered so successfully by Bülbring[1] for intestinal and other smooth muscle. There is no doubt that the system of classification of adrenoceptors proposed by Ahlquist[2] has made the discussion of adrenoceptor mechanisms a good deal more straightforward.

Smooth muscle from several different sites in the body has been used for electrophysiological studies. It soon became apparent that the cells behave as a syncytium with overall cable properties. Morphological studies revealed differences between muscles from different organs in the manner of local innervation, ranging from relatively sparse innervation in which muscle cells were distant from direct nervous influence, to dense innervation with frequent, close contact between nerve terminals and muscle cells. The functional implications of syncytial behaviour and innervation density were generally in line with the broad classification into multi-unit or unitary organisation[3,4].

Microelectrode measurements of resting membrane potentials revealed a mainly K dependent potential whereas the action potential was established to be

due to the entry of Ca ions from a membrane bound source. It also became apparent that Ca entry controlled membrane permeability to other ions and was intimately involved in the contractile process[5].

The mechanical activity of the smooth muscle, evidenced by the degree of tone it exhibited, by episodes of contraction or relaxation and by periods of spontaneous rhythmicity or quiescence, was found to be related to the state of the membrane potential and the rate of action potential discharge. With the investigation of a wide range of tissues it became clear that there is variability between different smooth muscle tissues: it is against this background of variability that the actions of the catecholamine adrenoceptor agonists have been investigated[6].

Activation of β-adrenoceptors induces relaxation or quiescence in all smooth muscle whereas activation of α-adrenoceptors induces contraction or relaxation depending on the site of origin of the muscle or even, for the uterus, on the hormonal environment to which the muscle has been exposed.

For intestinal smooth muscle the activation of α or β receptors is followed by relaxation but measurements of the electrophysiological and ionic changes accompanying the effect have revealed fundamental differences of mechanism. Agonists at α-adrenoceptors induce hyperpolarisation accompanied by an increase in K conductance, the membrane potential falls below the threshold for initiation of action potentials. Agonists at β-adrenoceptors suppress the slow depolarisation which generates the action potentials, there is little or no change in membrane potential and the tension response to action potentials is diminished so there may also be a decrease in excitation-contraction coupling.

The effects of stimulating β-adrenoceptors seem to be the same in all smooth muscles but the changes in membrane conductance caused by stimulation of α-adrenoceptors seem to involve different ions in different muscles.

Ultimately both α- and β-adrenoceptor stimulation involve the cellular distribution of Ca. Activation of α-adrenoceptors increases Ca permeability of the cell and the changes in membrane conductance produced by Ca are the same as those of α-adrenoceptor stimulation. Activation of β-adrenoceptors decreases the Ca permeability of the cell, the reduction in tension produced by β-adrenoceptor stimulation is opposed by Ca.

Bülbring (1973)[6] brought all these effects together in a summary hypothesis by suggesting that β-adrenoceptor activation reduces intracellular Ca available for the contractile mechanism by increasing the intracellular binding of Ca through an action of cyclic AMP in increasing the phosphorylation of a

protein, whereas α-adrenoceptor activation phosphorylates another protein (utilising ATP from a pool common with that involved in β-adrenoceptor activation) to cause release of Ca from membrane bound sites to change membrane conductance.

The investigation of liver cells has also involved studies on membrane permeability and on cell function, chiefly carbohydrate metabolism[7]. Although the liver comprises mainly parenchymal cells, or hepatocytes, it does contain a small proportion of other cells (eg. Kupffer cells) which may complicate studies on whole liver or liver slices. More recent use of isolated hepatocytes is an attempt to remove some of the difficulties. Although there are experimental variations yet to be resolved, which may have differences in technique or species as a basis for their explanation, in general it appears that hyperpolarisation of the membrane is the response to α- or β-adrenoceptor activation. The hyperpolarisation accompanying α-adrenoceptor activation is associated with an efflux of K from the cell[8].

Classically the β-adrenoceptor has been shown to mediate glycogenolysis which is associated with a rise in cyclic AMP, but it has recently been found that increased glycogenolysis can follow α-adrenoceptor stimulation too[9] which has led to speculation on the possible convergence of the effects of activation of these receptors. The classification of adrenoreceptors on hepatocytes has proved not to be straightforward because of inconsistencies in the potencies of antagonists when they are compared with those found on other peripheral tissues.

Most work on exocrine glands has been done on salivary glands and the pancreas and again the microelectrode has played a major role since the classical work of Lundberg (1958)[10]. Although most attention has been given to cholinergic innervation and the effects of hormones, the action of catecholamines has not been ignored[11]. The initial technical difficulties in measuring resting membrane potentials seem to have been resolved in the conclusion that they are not very different from those of nerve or muscle. As in smooth muscle and the liver, gland cells seem to be electrically coupled, with the coupling in exocrine glands such as salivary gland and pancreas, confined to a single acinus. The resting membrane potential like that of smooth muscle cells, is mainly due to the K diffusion potential. In many gland cells, for example salivary acinar cells, a secretory stimulus is associated with hyperpolarisation, and the hyperpolarisation induced by acetylcholine is associated with increased K permeability. Sympathetic stimulation produces a more transient hyperpolarisation than acetylcholine.