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Atrial Receptors

R.J. LINDEN AND
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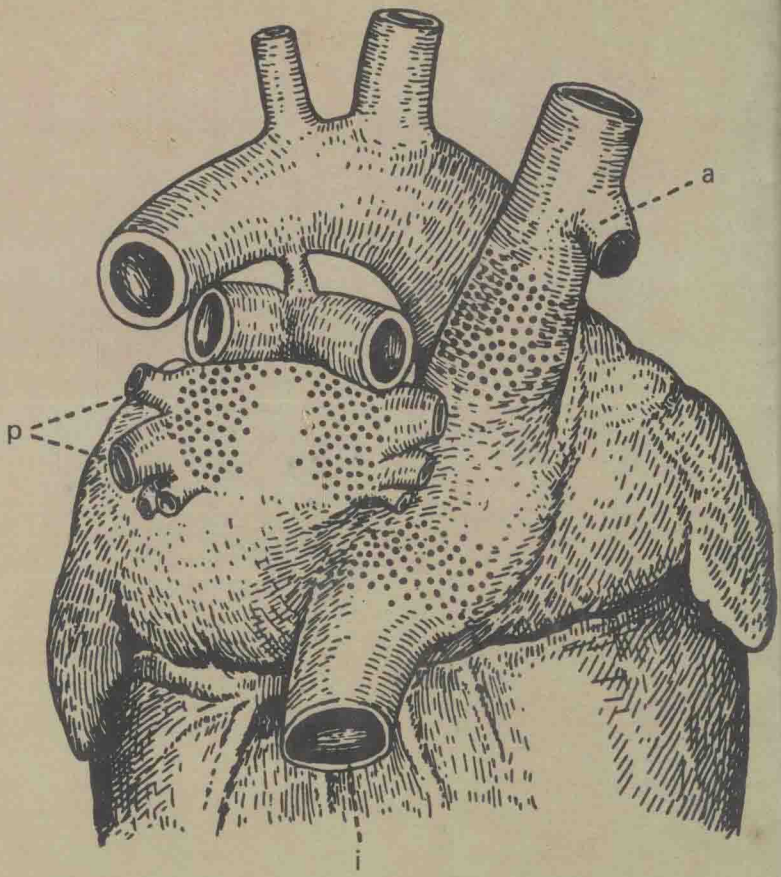

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ATRIAL RECEPTORS

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PREFACE

The interest in cardiovascular reflexes took an immense leap forward with the publication of the monograph *Reflexogenic Areas of the Cardiovascular System* by Heymans & Neil in 1958. The main topics of that monograph rightly concerned the functions of systemic arterial baroreceptors and chemoreceptors. Any reflexes thought to be emanating from the heart, such as the Bainbridge reflex, were confined under a heading 'Cardiovascular Reflexes of Uncertain Origin'; and others, complex in nature, were said to be evoked by the injection of large quantities of drugs.

However, as pointed out, it had been known since the turn of the century that nervous end-organs, the histological description of which led the investigators to believe they were physiological receptors, had been discovered in most tissues in the heart. Thus interest in the function of cardiac receptors was re-awakened. Following this review and the experiments in which various drugs were injected into vessels near or in the heart in attempts to stimulate receptors, numerous investigators examined the functions of cardiac receptors with varying degrees of success. Obviously a suitable division of approach was to examine, separately if possible, the functions of receptors in the ventricles and the atria. Brief comment is made in this monograph on the functions of ventricular receptors as they have been investigated extensively physiologically, though not histologically, and the information is necessary background for a consideration of the function of atrial receptors. However, the main topic of this monograph, atrial receptors, has only recently become of interest but, as shown in Chapter 2, they were well described histologically many years ago. Much of their function, as described in Chapters 6 and 10, has been shown by discrete stimulation of the receptors, but some, for the present, must be

a matter of conjecture and extrapolation based on the known functions of ventricular receptors as described in Chapter 7. However, a story of reflex mechanisms involving atrial receptors, heart rate and urine flow is unfolding and is presented in this monograph.

As the results of experiments in whole animal preparations depend so much on the 'state' of the anaesthetised preparation some space has been allocated (particularly in Chapter 4, but throughout) to brief descriptions of laboratory practice, usually based on evidence, but often on experience alone. Without this comment it would not be possible for the reader to make adequate judgements on the posed explanations of differences, sometimes qualitatively diametrically opposite, between the results obtained by different investigators.

Following the first chapter which simply indicates some of the means available to obtain evidence of the existence of reflexes from atrial receptors and also, in anticipation, states the main conclusions as to their function, the chapters sequentially present a view of atrial receptors from different aspects, each chapter building on the previous one. In order are presented comments on histology, electrophysiology, reflex effects on heart, circulation and kidney and finally speculation on possible clinical implications. Sufficient repetition and cross references have been provided to allow each chapter to have its own entity.

I am grateful for helpful discussion before, during and after experiments, to all my colleagues in the Department of Cardiovascular Studies, and particularly to Dr Kappagoda who not only was a close colleague during many of the investigations, but as co-author of this monograph also helped with the early drafts of some chapters of this monograph which was conceived during Dr Kappagoda's stay in Leeds and completed after his departure for Canada. It is with great pleasure I place on record my thanks to Drs Hainsworth, Kidd and Mary, each of whom helped during the later stages of the preparation of this monograph. I am also indebted to the many authors and publishers who allowed reproduction of material and to the secretarial help who patiently reproduced copy after copy of the manuscript, without complaint.

Leeds R. J. L.

CONTENTS

1 INTRODUCTION TO THE REFLEX RESPONSES FROM THE ATRIA

The main object of this monograph is to consider the evidence for and against the presence of different types of nervous end-organs, receptors, in the atria and, as will appear, to attribute reflex function to them. A first consideration must be what a reflex is and the criteria, anatomical and experimental, which warrant the conclusion that effective reflexes exist.

The consideration of a reflex

In physiological terms, the word *reflex* has a specific meaning. It involves the application of an adequate stimulus to a receptor, the activation of which results in the transmission of impulses in afferent nerves into the central nervous system (CNS). This 'information' is then 'processed' in the CNS with the subsequent transmission of impulses in efferent nerves to an effector organ resulting in the response. Thus the anatomical basis for a reflex is a reflex arc. In designing experiments to investigate reflex mechanisms, particular attention has to be paid to the component parts of the reflex arc.

Receptor

The receptor in any reflex arc is physiologically attached to an afferent nerve and it is specifically stimulated to discharge by some change in its environment. Thus its function is to lower the threshold of that fibre to one form of energy. No attempts have yet been made to study the precise mechanisms responsible for the initiation of the impulse at the endings in the atrial endocardium, a point emphasised by Paintal (1972) who, in his comments on this process in atrial receptors, extrapolated from investigations of the Pacinian corpuscle. However, it is important

to realise that the fibro-elastic tissues in which the receptors lie probably determine the main individual characteristics of the 'receptor area'.

The receptor is usually recognised histologically, e.g. the unencapsulated endings in the atrial sub-endocardial tissue (see Chapter 2), but often may be unknown histologically and be recognised physiologically by its discharge characteristics in terms of the pattern of trains of impulses in its afferent nerve, e.g. see the evidence for a second and third group of receptors in the atrial wall which are known to discharge into the vagal and sympathetic nerves (see Chapter 3).

Other characteristics of a receptor involve a description of the adequate stimulus to it which evokes the response. Such a description may be in simple terms usually used in physiological texts when describing reflex functions or it could be in engineering terms involved in control theory (e.g. Milhorn, 1966; Guyton, Coleman & Granger, 1972). The former would involve the relationship of numbers, frequency and patterns of impulses to pressure, stretch and chemical stimuli, whilst the latter would demand these relationships be computed as transfer functions. However, as the atrial receptors and their function have not yet been investigated from the standpoint of control theory there will be no further consideration of this topic in this monograph.

Afferent nerve

The afferent nerve fibres involved in the reflexes from the atria may be large or small, myelinated or non-myelinated and are usually recognised by their conduction velocities, which characterise one group of myelinated fibres in the vagi (conduction velocities 9–35 $m \cdot s^{-1}$) as emanating from unencapsulated endings in the sub-endocardial tissue. Of the other two groups, both without known histological end-organs, one discharges into non-myelinated fibres (conduction velocities $< 2\ m \cdot s^{-1}$) in the vagi, and the other into both myelinated (conduction velocities 5–25 $m \cdot s^{-1}$) and non-myelinated fibres (conduction velocities $< 2\ m \cdot s^{-1}$) which pass into the spinal cord through the rami communicantes, the so-called 'sympathetic' afferent fibres. These three groups of fibres and some of the functions

attributed to them will be referred to again in subsequent chapters – particularly Chapters 3, 6, 7 and 10.

Techniques, dependent on the above properties, of cooling (e.g. Kappagoda, Linden & Sivananthan, 1979) and anodal block (e.g. Coleridge, Coleridge, Rosenthal & Dangel, 1973) are also used for the recognition of specific afferent fibres involved in particular reflex responses and the value of these techniques will also be discussed in Chapters 4, 6, 7 and 10.

Efferent limbs of a reflex

Where the efferent limb of the reflex is in peripheral nerves, the efferent fibres are recognised by techniques similar to those by which afferent fibres are observed. In addition, there is a possibility of obtaining the response and blocking the effect on the effector organ. For instance, when the response of the reflex is a change in heart rate caused by a change in the activity in the efferent sympathetic nerves, then as well as being able to section the nerves to abolish the response after first demonstrating its presence, it is always possible to use a β-adrenoreceptor antagonist to block the effect of the liberated noradrenaline at the receptor sites on the effector organ. This technique and other similar ones will be described in Chapters 4, 6 and 7.

Effector organ

In general this is the most obvious functional part of any reflex as changes in it are observed when measuring the response. For instance changes in the heart rate are easy to observe on a record of systemic arterial blood pressure or electrocardiogram and heart rate can be shown to change on applying the stimulus; such a response in the heart to stimulation of atrial receptors, and other responses in the kidney, will be described in Chapters 6 and 10.

Central nervous connections

This portion of a reflex arc is the hardest to define and research in this area usually awaits a fairly complete description of the

parts of the reflex arc enumerated above. Little is known of the central connections of the reflexes attributable to atrial receptors because research in this area is only just beginning, but the evidence available will be described and criticised in Chapters 8 and 10.

The reflexes from atrial receptors

The evidence from some of the results of investigations into the function of atrial receptors has been anticipated in that it has been stated above that there are three distinct groups of receptors.

To anticipate further the contents of this monograph evidence will be provided to substantiate the above grouping of receptors and to support the following functions.

Much the most investigated of the groups of receptors are the unencapsulated end-organs within the sub-endocardial tissues which discharge into myelinated fibres in the vagi. Stimulation of these receptors results in a reflex increase in heart rate, with afferent fibres solely in myelinated fibres in the vagi, central connections in the medulla, an efferent pathway solely in sympathetic nerves to the heart and there is no concomitant positive inotropic effect. In addition, they cause a reflex increase in urine flow with a small increase in sodium excretion; the efferent limb of this reflex is both nervous and hormonal. The hormonal limb consists of a substance which is not the antidiuretic hormone (ADH), and is possibly a diuretic substance; the possibility that there may be a small change in the concentration of ADH in the plasma is not yet completely decided. The blood-borne agent causes only an excretion of water and not sodium. The inhibition of the activity in efferent renal nerves caused by stimulating atrial receptors results in a small increase in water excretion and is the main cause of the increase in sodium excretion. Some increase in water and sodium excretion may be caused by haemodynamic changes secondary to the increase in heart rate. Evidence for these conclusions will be presented and discussed in Chapters 3, 4, 6 and 10.

There is much less evidence for the function of the other two groups of atrial receptors mainly because they have only recently