PERIPHERAL ACTIONS OF DOPAMINE

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PERIPHERAL ACTIONS OF DOPAMINE

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Contents

<i>Preface</i>	vii
<i>Abbreviations</i>	xi
<i>Conference Participants</i>	xiii
1 Sources of Circulating Dopamine: A Personal View <i>J.-L. Cuche</i>	1
2 Dopamine Storage in Sympathetic Nerves <i>P. Soares-da-Silva</i>	24
3 Neurochemistry of Dopaminergic Nerves <i>C. Bell, M. Ferguson and T. Petrovic</i>	41
4 Release of Dopamine from the Kidney <i>in vivo</i> <i>P. Hjendahl, T. Bradley and B. Tidgren</i>	56
5 Dopamine and Renal Failure <i>W. R. Adam</i>	75
6 Dopamine and Hypertension <i>M. Yoshimura and H. Takahashi</i>	94
7 The Vascular (DA ₁) Dopamine Receptor <i>J. D. Kohli and L. I. Goldberg</i>	108
8 Renal Dopamine Receptors <i>R. A. Felder, C. C. Felder, G. M. Eisner and P. A. Jose</i>	124
9 Gastrointestinal Dopamine Receptors <i>R. A. Lefebvre</i>	141
10 Neuronal Dopamine Receptors <i>M. F. Lokhandwala and M. L. Defeo</i>	153
11 Drug Design for Cardiovascular Therapeutics: Activation of DA ₁ Receptors <i>B. A. Berkowitz</i>	174
12 Use of Dopamine Agonists in Cardiovascular Disease <i>B. P. McGrath, N. Sano and B. F. Jover</i>	186

13	Modified Dopamine Agonists	<i>R. D. Hoskins, R. A. Brown, R. A. Foulds, F. Ince, S. O'Connor and G. W. Smith</i>	197
14	Dopamine Pro-Drugs	<i>M. R. Lee</i>	207
	<i>Summary of Conference Proceedings</i>		219
	<i>Index</i>		225

Preface

Dopamine (DA) has been recognised for many years as the synthetic precursor of noradrenaline, but its low potency as an adrenoceptor agonist led to the general presumption that it had no independent biological role in the periphery, despite acceptance that specific dopaminergic neurons existed in the central nervous system.

The first hint that DA might subserve a peripheral physiological role came from the demonstration that vasodilator receptors for the molecule existed in a few vascular beds, independent of adrenoceptors: these DA receptors appeared to be most concentrated in the vasculature of the kidney. In turn, knowledge of existence of the DA receptor led to experiments designed to ascertain whether these receptors are activated by endogenous DA.

Analysis of the actions of DA in the body has been both facilitated and hindered by the close chemical similarity between DA and the other endogenous catecholamines. The extensive background knowledge of catecholamine synthesis and turnover, the existence of techniques for their detection in picomolar quantities, and the availability of numerous pharmacological tools for manipulating synthesis, release and action, have enabled research on DA to proceed far more rapidly than has been the case with a number of other putative peripheral messengers, such as the peptides. On the other hand, the same close similarity between all three catecholamines necessarily results in some similarities of biological activity, and, until recently, neither DA agonists nor DA antagonists had been available with adequate selectivity for DA receptors to allow confident analysis of its specific activity at DA receptors. As well, the ubiquitous presence of DA as a precursor at sites of noradrenaline synthesis has often made it difficult to be sure that changes in DA stores, or the occurrence of DA-mediated events, are independent of events primarily involving noradrenaline.

Despite these difficulties, a remarkable amount of evidence has accumulated over the last several years to indicate that DA has very powerful effects

on some peripheral physiological parameters, particularly in the cardiovascular and renal systems. As well, there is increasing evidence that deficiency of either release or action of endogenous DA in the kidney is an important pathophysiological factor contributing to the reduced renal function in essential hypertension and renal failure. These findings have opened up exciting new vistas for the understanding and treatment of a variety of disease states, with considerable socio-economic implications. It is therefore an appropriate time to review the current state of thinking about the actions and significance of DA in the periphery. With this in mind, representatives of international research groups active in the field met for two days in Melbourne in August of 1987, to exchange ideas and recent results, and to plan strategies for the future. This book represents a synthesis of their discussions.

The subject areas covered can be divided into three broad categories.

The first relates to the sources and effects of endogenous DA (Chapters 1–5). The questions of whether circulating DA is of neuronal or extraneuronal origin, and the roles of DA in sympathetic nerve function, are addressed. These matters lead on to consideration of the probable physiological significance of DA in renal function and salt balance, and its possible aetiological role in renal failure and hypertension.

The second section of the book deals with the classification and distribution of, and the effects of activating, various populations of peripheral DA receptors (Chapters 7–10). Specific attention is paid to the validity of differentiating between DA₁ and DA₂ receptors (also referred to here as DA-1 and DA-2 in some chapters), as has been done for the D₁ and D₂ receptors of the central nervous system, and to the effects of DA receptor activation in the kidney, the gastrointestinal tract and various blood vessels, and at sites on post-ganglionic sympathetic nerves.

Finally, the therapeutic significance of DA receptor activation in cardiovascular and renal disease is examined from a number of standpoints (Chapters 11–14). Included here are considerations of the different pharmaceutical philosophies which can be utilised in the development of appropriate therapeutic agents, and evaluation of the various pharmacological agents by which cardiovascular DA receptors can be activated.

The transcripts of a meeting are frequently of interest more to the participants than to the average reader, so we have made no effort to reproduce in full the discussions which occupied a major part of the conference, although we have attempted to select the salient points of interest from the discussion transcripts. Our aim has not been to produce a compendium of recent research results, but rather a resource kit for indicating the current state of various aspects of peripheral DA research; and we asked the contributors of chapters to bear this in mind when preparing their manuscripts.

The meeting on which the volume is based was financially supported by Fisons Pty Ltd, Smith Kline Beckman, the Ian Potter Foundation, Smith, Kline and French Research Ltd and Abbott Laboratories, and we wish to express our thanks to all these bodies. As well, the University of Melbourne generously provided the physical facilities for the meeting, and Mrs Kerry-Ann Bayliss gave excellent secretarial assistance. We also wish to thank The Macmillan Press for agreeing to publish the book, and for the expedition with which this has been achieved.

Victoria, Australia, 1988

C. B.
B. McG.

Abbreviations

Throughout this book the following abbreviations have been used for frequently used words:

ADR	Adrenaline (epinephrine)
ANG II	Angiotensin II
ANP	Atrial natriuretic peptide
cAMP	Cyclic adenosine monophosphate
DA	Dopamine
DBH	Dopamine β -hydroxylase
DCT	Distal convoluted tubule
DOPA	3-(3,4-dihydroxyphenyl)alanine
IG	Intragastric
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NA	Noradrenaline (norepinephrine)
PCT	Proximal convoluted tubule
PNMT	Phenylethanolamine- <i>N</i> -methyltransferase
3-PPP	3-(3-hydroxyphenyl)- <i>N</i> -n-propylpiperidine
PRA	Plasma renin activity
PRU	Peripheral resistance units
PST	Phenolsulphotransferase (Chapter 1) Proximal straight tubule (Chapter 8)
SHR	Spontaneous hypertensive rat
WKY	Wistar Kyoto rat

All other abbreviations used by specific authors have been defined at their first use in the chapter concerned.

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