VOLUME 10

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David G. Reynolds
H. Richard Adams

ADVANCES IN SHOCK RESEARCH

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VOLUME 10

Proceedings of the Fifth Annual Conference on Shock
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Part 2

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ADVANCES IN SHOCK RESEARCH

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Contents of Volume 9

Part 1 of the Proceedings of the Fifth Annual Conference on Shock

Preface

Pharmacologic approaches to problem-solving in circulation research were addressed during the 5th Annual Conference on Shock held by the Shock Society at Smugglers' Notch, Vermont, June 9–11, 1982. Two separate symposia and several independent research papers dealing directly or indirectly with drug-related topics were presented, and the manuscripts derived from these presentations comprise Volume 10 of Advances in Shock Research.

The first symposium was entitled "Pharmacologic Problems in Shock " and five separate papers considered positive and negative aspects about several drug groups important to cardiovascular research in general with emphasis on shock research in particular. The introductory presentation in this collection assumed the "devil's advocate" position, relative to the employment of drugs as experimental tools, and pointed out how interpretations of drug-based data can be inadvertently oversimplified if subsidiary biologic actions of tested compounds escape attention. Subsequent talks in this symposium considered pros and cons about drugs that inhibit synthesis of prostanoid metabolites of arachidonate; free-radical formation in shock and free-radical scavenging agents; and the use and misuse of inotropic drugs employed in the therapeutic management of cardiogenic shock. The drug group known originally as "calcium antagonists" but now more appropriately named as "calcium channel blockers" or "calcium entry blockers" was also addressed and this presentation provided a preview of how this "new" group of important compounds may be applied to shock research.

The second symposium focused entirely on "The Role of Endogenous Opiates in Shock," a subject that has arisen only within the past few years. This area of research entails a new concept that endogenous opiates contribute to cardiovascular dysfunction in shock. Opiate receptor antagonists have been used to test the hypothesis and the data presented indicate that agents such as naloxone not only improve cardiovascular function but also improve longterm survival. The symposium consists of six papers that considered opiate mechanisms involved in hemorrhagic and endotoxic shock and spinal trauma in a broad spectrum of animal models; an evaluation of areas of the central nervous system involved in the mechanism; opiate-endocrine interactions; peripheral effects of opiate antagonists in shock; and putative clinical applications of the experimental findings. The symposium is the first to be devoted to the subject.

A group of independent research papers reemphasized the ongoing interest in opioid agonists and antagonists, and brought new insight about possible species differences in the effects of opioid antagonists in stress situations. Similarly,

several presentations provided more data to the growing volume of information about non-steroidal anti-inflammatory drugs used in attempts to modify synthesis of the prostaglandin cascade. Other papers continued the search for a resolution of benefit-risk ratios associated with the use of adrenal corticosteroids in low-flow and shock states.

The content of this volume is significant from at least three points of view. First, a critical evaluation of the use of pharmacological agents in shock research is an exercise that should be practiced frequently by those engaged in such research. Secondly, the subject of opiate mechanisms in shock is presented in a manner to explain the rationale of the concept. Lastly, the information presented on the formation of free-radicals in shock introduces the concept that the enzyme, superoxide dismutase, could have a role in shock therapy. Further significant work in this last area will surely be forthcoming.

The editors wish to thank Nancy M. Bailey for her editorial and secretarial assistance in the preparation of this volume.

Sherwood M. Reichard
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H. Richard Adams

Contents

PHARMACOLOGIC PROBLEMS IN SHOCK

(Papers in this section were presented in a Symposium at the Fifth Annual Conference on Shock)

Advances in Shock Research 10:3–8 (1983)

Pharmacologic Problems in Shock Research

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Recent advances with receptor-selective agonists and antagonists have provided great impetus to the deployment of drugs as experimental tools in cardiovascular research. Often overlooked, however, is the important limitation that few exogenous chemicals actually exert only one biologic action. This discussion appraised several prototype drugs used in this field, and theorized how a lack of consideration of subsidiary pharmacologic actions may lead to oversimplified interpretations of drug-based data.

INTRODUCTION

Pharmacologic agents are used commonly in shock research as investigators attempt to identify and characterize pathogenic mechanisms involved in circulatory shock syndromes. Application of drugs as experimental probes is based on the premise that specificity of drug action provides the means to chemically modulate only selected physiologic-pathophysiologic events, leading in turn to the delineation of particular functions-dysfunctions as important components of shock. Indeed, as reported in subsequent papers in this volume, experimental use of drugs has provided new insight into organ and cellular control mechanisms operating in the pathogenic response to shock-inducing stimuli.

A potential danger to this type of pharmacologic approach is the inherent, but often overlooked, limitation that many drugs assumed to be mechanistically specific actually exert multiple biologic influences. This criticism is valid irrespective of the routine classification of drug groups according to a single pharmacologic action. If drug-based data are interpolated into new concepts too quickly, validation of the relative importance of primary vs subsidiary pharmacologic actions may be neglected and the operational value of the concept may suffer.

Perhaps the use of drugs as experimental implements should be considered a double-edged sword, leading to new insight and concepts on one edge but potentially leading to oversimplification of cause-effect relationships on the

other edge. Examples of this type of problem can be formulated from a brief overview of pharmacodynamic complexities of several drugs important to cardiovascular research.

ALPHA-ADRENERGIC BLOCKING AGENTS

Sympathoadrenal activation of alpha adrenergic mechanisms has long been implicated in the pathogenesis of shock [cf 1, 2]. This important concept was based on several lines of evidence, including observations that drugs which prevented alpha-adrenergic responses also prevented or delayed death in shock. In essence, it was concluded that alpha antagonists were beneficial because they blocked alpha receptor-mediated vasoconstriction, thereby improving microcirculation and reducing the stagnant hypoxia of shock [1, 2].

Recent discoveries in adrenergic physiology-pharmacology have shown that the net circulatory response to alpha blocking drugs cannot be explained solely by an inhibitory action at alpha receptors subserving vascular smooth muscle contraction [3–5]. Direct and indirect influences on other receptor populations, both alpha and beta, should also be considered.

Alpha-adrenergic receptors can now be differentiated into two distinct subtypes designated $alpha_1$ and $alpha_2$ [4–6]. $Alpha_1$ receptors represent the more classical alpha-receptor population; they are located postjunctionally on effector cells and are blocked more potently by prazosin than yohimbine. $Alpha_2$ receptors are newly discovered; they are localized prejunctionally on neuron terminals and also postjunctionally on some effector cell types, and are blocked more potently by yohimbine than prazosin. Norepinephrine and epinephrine activate both $alpha_1$ and $alpha_2$ receptors, whereas phentolamine and phenoxybenzamine block both $alpha_1$ and $alpha_2$ receptors [5, 6].

$Alpha_2$ receptors of noradrenergic neurons subserve an important autoinhibitory effect on norepinephrine release mechanisms [3]. Norepinephrine discharged from the nerve terminal can feed back and activate prejunctional $alpha_2$ receptors, resulting in a dimunition of subsequent neuroeffector transmission. On the other hand, nonselective $alpha_1$-$alpha_2$ blocking drugs inhibit alpha-mediated events in effector organs, but they also facilitate catecholamine release by freeing noradrenergic nerves from the $alpha_2$ feedback inhibition [3–7].

Thus, it seems that cardiovascular responses to nonselective $alpha_1$-$alpha_2$ antagonists may be more faceted than originally surmised. Evidence now shows that these drugs do not simply prevent alpha-controlled events in effector organs. Because of their prejunctional $alpha_2$ blocking action, they also free or disinhibit catecholamine release mechanisms from a resident inhibitory control. This action elicits a substantial increase in circulating catecholamines [7] and perhaps even a relatively greater increment in nor-