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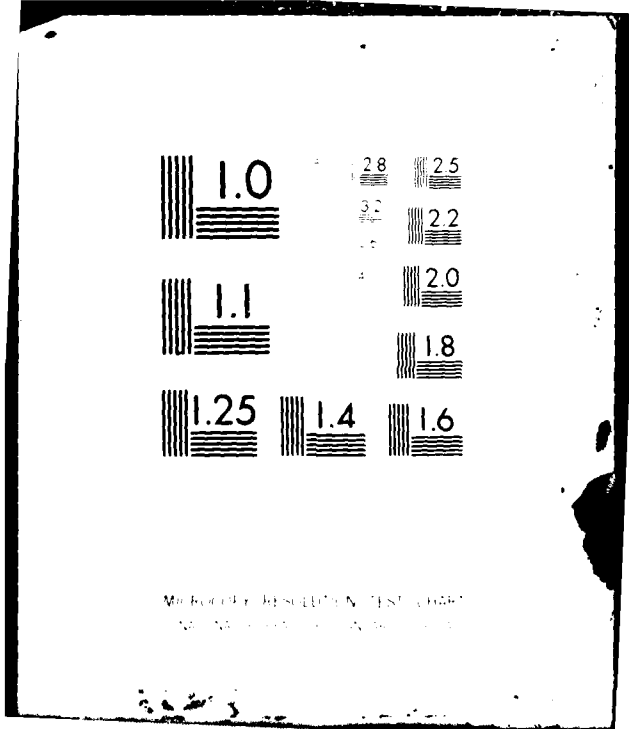
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Lethal or near-lethal doses of acetylcholinesterase (AChE) inhibitors cause respiratory depression and cardiovascular collapse. Lower doses, however, evoke a centrally-mediated increase in blood pressure. This hypertensive response occurs in a variety of animal species, including humans. The overall objective of this project was to study the central mechanisms involved in the pressor effect of AChE inhibitors and to determine the role of brain acetylcholine (ACh) in hypertensive states. To that end I believe the project was quite

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20. ABSTRACT CONTINUED

successful. We have defined the role of brain ACh in the central regulation of baroreceptor reflexes and have localized the site of this effect to the posterior hypothalamic nucleus. In addition, we have shown that in the spontaneously hypertensive rat, which appears to have enhanced central cholinergic activity, brain ACh is involved in maintaining the elevated blood pressure. As an offshoot of this project this last finding suggests new directions for antihypertensive therapy.

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HYPERTENSIVE EFFECT OF BRAIN ACETYLCHOLINESTERASE INHIBITION

FINAL REPORT

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8 March 1982

U.S. ARMY RESEARCH OFFICE

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I. OBJECTIVES

Lethal or near-lethal doses of acetylcholinesterase (AChE) inhibitors cause respiratory depression and cardiovascular collapse. Lower doses, however, evoke a centrally-mediated increase in blood pressure. This hypertensive response occurs in a variety of animal species, including humans.

The overall objective of this project was to study the central mechanisms involved in the pressor effect of AChE inhibitors and to determine the role of brain acetylcholine (ACh) in hypertensive states. To that end I believe the project was quite successful. We have defined the role of brain ACh in the central regulation of baroreceptor reflexes and have localized the site of this effect to the posterior hypothalamic nucleus. In addition, we have shown that in the spontaneously hypertensive rat, which appears to have enhanced central cholinergic activity, brain ACh is involved in maintaining the elevated blood pressure. As an offshoot of this project this last finding suggests new directions for antihypertensive therapy.

The work done in this study has resulted in six publications and four abstracts. In addition, a 40 page invited review of central cholinergic control of blood pressure was written for Annual Review of Pharmacology and Toxicology and will appear in the 1982 edition sometime in April.

II. FINDINGS

A. Peripheral Vascular Responses

While examining the peripheral mechanisms involved in the hypertensive effect of physostigmine we observed that the β -adrenergic blocking agent, propranolol, evoked a marked elevation of blood pressure in rats treated with α -adrenergic blockers such as phentolamine. Furthermore, in rats which were either adrenalectomized or pretreated with propranolol the subsequent administration of phentolamine caused little or no reduction in blood pressure. Since arterial pressure is one of the primary endpoints in our research we felt it necessary to understand the mechanism and physiological significance of these findings.

Our studies revealed a complex series of events which occurs in response to α -adrenergic receptor blockade. The loss of sympathetic tone and resultant fall in blood pressure, in addition to the block of presynaptic α -receptors, leads to increased sympathetic activity and a release of adrenal catecholamines. Subsequent action of these catecholamines on vascular β -receptors adds to the initial vasodilation. On the other hand, the increased sympathetic stimulation of renal β -receptors leads to an opposing vasoconstriction through activation of the renin-angiotensin system. Under normal circumstances the vasodilation predominates. However, administration of a β -adrenergic blocking agent at this time prevents the epinephrine-induced vasodilation and an angiotensin-mediated elevation of blood pressure ensues. The sympathetic discharge induced by phentolamine also stimulates renin release in rats which have undergone acute adrenal demedullation. In the absence of circulating epinephrine angiotensin maintains the blood pressure near normal levels. Thus, administration of α - or β -adrenergic blocking

agents induces reflex changes in the sympathetic and renin-angiotensin systems which may be masked by the direct actions of these drugs. Under certain conditions these reflexes may be unmasked and may influence the outcome of an experimental or clinical situation.

B. Baroreceptors

1. Reflex changes in heart rate

In unanesthetized rats injection of physostigmine into the lateral cerebral ventricle evokes an increase in basal blood pressure and a decrease in heart rate, along with a potentiation of reflex bradycardia and an inhibition of reflex tachycardia. These effects of physostigmine are blocked by atropine or by doses of hemicholinium-3 which deplete ACh stores in the brain. In addition, hemicholinium-3, by itself, inhibits both reflex bradycardia and tachycardia.

2. Carotid artery occlusion reflex

Bilateral occlusion of the common carotid arteries decreases the pressure on the carotid sinus baroreceptors, resulting in an increased sympathetic discharge and a subsequent increase in blood pressure. Injection of physostigmine either i.v., into the lateral cerebral ventricle or into the posterior hypothalamic nucleus causes a marked potentiation of this response. Likewise, injection of neostigmine into the cerebral ventricles or posterior hypothalamus increases the magnitude of the carotid occlusion reflex. In each case basal arterial blood pressure also increases.

Neostigmine was shown to be about 60 times more potent than physostigmine (on a molar basis) in potentiating the carotid occlusion reflex or in elevating basal blood pressure. This is consistent with its greater ability to inhibit brain AChE following intracerebroventricular (icv) injection. On the basis of our previous finding that in vitro neostigmine is only about 5 times more potent than physostigmine the greater difference in vivo may reflect differences in distribution of the two drugs.

Both atropine and icv injection of hemicholinium-3 prevented the potentiating effect of the AChE inhibitors on the carotid occlusion pressor reflex. Of considerable significance was the finding that bilateral injections of atropine into the posterior hypothalamic nucleus blocked the potentiating effect of intravenously injected physostigmine. This indicates that the posterior hypothalamus contains the final muscarinic synapse in the central circuit potentiating the carotid occlusion pressor reflex. The increase in basal blood pressure produced by i.v. physostigmine was not inhibited by intrahypothalamic injections of atropine, indicating that this response is generated at some other site. We previously have suggested the brainstem as the source of the pressor response.

C. Hypertension

Since central cholinergic stimulation evokes an increase in blood pressure we sought to determine how animals with chronically elevated blood pressures respond to interference with cholinergic function in the brain. Experiments were carried out in the spontaneously hypertensive rat (SHR), a genetic model of hypertension which is well studied and for which there is evidence of increased central cholinergic activity.

Intravenous injection of atropine, but not of methyl atropine, caused a dose and age-related fall in blood pressure in the SHR. The threshold dose in adult animals was between 0.2 and 0.5 mg/Kg. In those experiments the hypotensive response was short-lived, lasting about 30 minutes. More recent experiments using non-invasive measurement of blood pressure (tail-cuff occlusion) has revealed that the response can last 24 hours. Apparently cannulation (or ligation) of the carotid artery has some effect on this response. We have not explored further this finding.

In addition to atropine, injection of hemicholinium-3 into the cerebral ventricles causes a dose-dependent fall in blood pressure. Thus, interference with central cholinergic activity in the SHR, either by blockade of muscarinic receptors or reduction of ACh concentration, causes a decrease in blood pressure. This suggests that under certain circumstances elevated blood pressure may be maintained by increased central cholinergic activity.

More recently we have studied the possible antagonistic effects of a unique anticholinergic drug on the pressor response to physostigmine and on blood pressure in the SHR. The compound is N-(4-diethylamino-2-butynyl)-succinimide, also referred to as DKJ-21. This drug can block muscarinic receptors in the brain at doses which do not affect muscarinic receptors in peripheral tissues. Our preliminary studies have shown that i.v. injection of DKJ-21 inhibits the pressor response to physostigmine and causes a long-lasting reduction in blood pressure in the SHR. Pressor responses to norepinephrine or ganglionic stimulation are not impaired, indicating that peripheral autonomic function is intact. No hypotensive effect is seen in normotensive animals.

Experiments were begun on the role of brain ACh in stress-induced hypertension. A stress chamber, as described in the original grant application, was donated by a local pharmaceutical company. Unfortunately, our experience with this method of inducing hypertension was as unsuccessful as was theirs. We therefore resorted to immobilization stress. In this procedure, the rats are physically restrained for periods of up to 2.5 hours. Blood pressure increases by up to about 25 mm Hg. We anticipated that under stress brain ACh activity should increase and potentiate the cardiovascular effects of AChE inhibitors. Instead, we found no change or a slight reduction in the magnitude of the pressor response. This appears to be due to a decrease in the ability of released norepinephrine to cause vasoconstriction. The pressor response to norepinephrine under these circumstances is drastically reduced. Thus, it is likely that the central effect of physostigmine is potentiated but the pressor response is blunted by an effect of stress on responsiveness of the peripheral vasculature. Further experiments are necessary to clarify this situation.

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