

Central Cholinergic Stimulation Causes Adrenal Epinephrine Release

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Abstract. Cholinergic drugs administered into the cerebral ventricles of animals selectively stimulate the adrenal medulla. However, the effects of central cholinergic stimulation on the sympathoadrenal system have not been studied in man. We stimulated central cholinergic activity in man by administering the cholinesterase inhibitor physostigmine to subjects pretreated with peripheral cholinergic blocking agents. A dose of 0.022 mg/kg physostigmine dramatically increased plasma epinephrine levels and slightly increased norepinephrine levels, which is consistent with selective adrenomedullary stimulation. A smaller dose of physostigmine increased epinephrine but did not alter norepinephrine levels. Subjects had increased pulse rates and blood pressures, and felt anxious while they had high plasma epinephrine levels.

Introduction

Centrally active cholinomimetic drugs, including the cholinesterase inhibitor physostigmine and the cholinergic agonists carbachol, arecoline, and acetylcholine, raise blood pressure in a variety of animal species (1). Cholinergic agonists and cholinesterase inhibitors that fail to pass the blood-brain barrier, however, have no pressor effects, except when administered intracerebrally. These central cardiovascular effects appear to be mediated by muscarinic stimulation of the sympathoadrenal system, and can be blocked by centrally acting anticholinergic agents such as atropine, or by transecting the spinal cord rostral to the sympathetic outflow (2, 3).

When physostigmine is given centrally to rats, it increases blood pressure solely by liberation of adrenal catecholamines, since this effect is completely blocked by adrenalectomy (4).

Furthermore, central administration of carbachol increases blood levels of epinephrine to a greater extent than it increases norepinephrine (5). These findings suggest that central cholinergic stimulation primarily activates adrenomedullary pathways.

Although considerable evidence suggests that central cholinergic neurohormones increase blood pressure and epinephrine release in animals, very few studies have explored such effects of cholinomimetics in man (6, 7). We activated central cholinergic pathways in human subjects with physostigmine, and compared effects with those of placebo.

Methods

12 men aged 24 ± 4.2 yr (\pm SD) who weighed 73 ± 10 kg participated in the study after giving informed consent. All had normal medical histories, physical examinations, and mental-status examinations. For at least 1 h before infusion, the subjects rested in a quiet room, and had a cannula (butterfly needle) filled with dilute heparin inserted into an antecubital vein. Subjects were treated parenterally with 1.0 mg noncentrally acting methscopolamine 20 min before drug infusion or 45 mg propantheline orally 90 min before drug infusion, to prevent the peripheral effects of physostigmine. Six subjects were then infused with a high dose (0.022 mg/kg) and six with a low dose (0.4 mg) of physostigmine salicylate. 2 or more days before or later, they also received placebo, using a double-blind, crossover design. In a separate experiment, nine other subjects were infused with 0.011 mg/kg neostigmine. This dose is approximately equipotent to 0.022 mg/kg physostigmine in its peripheral anticholinesterase effects in dogs (8). It also has a similar LD-50 in rats and mice (The Merck Index, 1983, Merck & Co., Inc., Rahway, NJ). Physostigmine, neostigmine, and placebo were infused over a 10-min period. 20 min after the termination of the high dose physostigmine infusion, atropine (0.8 mg i.v.) was given to terminate the central muscarinic effects of physostigmine. Periodically, both pre- and post-infusion, blood samples were drawn from the indwelling cannula, heart rate was measured by palpation, and blood pressure was assessed by auscultation. Plasma epinephrine and norepinephrine levels were measured by the radioenzymatic method of Durrett and Ziegler (9), and dopamine-beta-hydroxylase (DBH)¹ was measured by the method of Molinoff et al. (10). Statistical significance was determined by the use of analysis of variance (ANOVA) techniques, comparing drug effects versus placebo effects for the blood pressure, DBH, and catecholamine levels obtained.

1. Abbreviations used in this paper: ANOVA, analysis of variance; DBH, dopamine-beta-hydroxylase.

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Results

20 min after infusion, high dose physostigmine significantly increased plasma epinephrine above base-line levels by 725 ± 286.5 pg/ml, and increased norepinephrine levels by 237 ± 70 pg/ml (Fig. 1). Epinephrine subsequently decreased by 40% from its peak after atropine administration, whereas norepinephrine returned to base-line levels.

High dose physostigmine also significantly increased heart rate (Fig. 2) and systolic and diastolic blood pressure levels (Fig. 3), and these cardiovascular effects decreased after atropine administration. In contrast, neostigmine (0.011 mg/kg) did not significantly alter plasma norepinephrine, epinephrine, blood pressure, or pulse rate. (Table I)

Low dose infusion of physostigmine (0.4 mg) increased epinephrine levels significantly (Fig. 4), but did not alter plasma norepinephrine or increase plasma DBH activity levels, heart rate or, systolic or diastolic blood pressure. Physostigmine tended to increase plasma DBH activity at the 20-min postinfusion time after both high and low dose physostigmine administration, but this effect did not reach statistical significance.

Discussion

Human sympathetic nerves release norepinephrine, but do not contain appreciable amounts of epinephrine. The catecholamine content of the human adrenal is 80% epinephrine, and normal adrenal effluent is 64% epinephrine and 36% norepinephrine (11). Infusion of equal amounts of epinephrine and norepinephrine lead to similar blood levels of these catecholamines (12). Thus, the high ratio of blood epinephrine to norepinephrine seen after physostigmine infusion suggests that physostigmine stimulates adrenal catecholamine release without appreciably enhancing norepinephrine release from sympathetic nerve endings.

As suggested by animal studies, the effect of physostigmine on the adrenal medulla appears to be centrally mediated, since

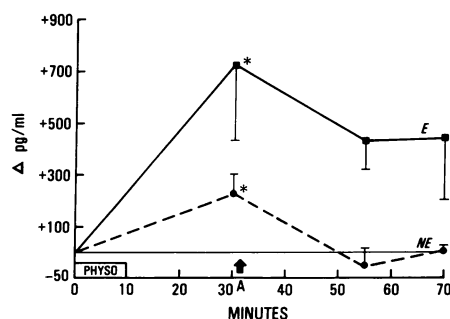


Figure 1. Changes in plasma concentration of E (■) and NE (●) after high dose (0.022 mg/kg) physostigmine (PHYSO). Values are means + SEM. Arrow indicates when atropine (0.8 mg) was given. * $P < 0.05$ by paired t test vs. preinfusion mean.

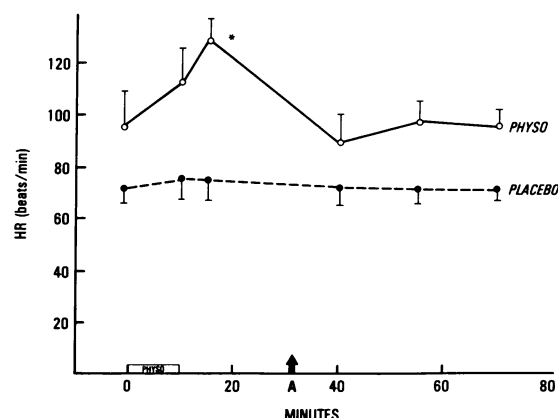


Figure 2. Heart rate after infusion of high dose (0.022 mg/kg) physostigmine (PHYSO; ○) and placebo (●). Arrow indicates when atropine (0.8 mg) was given. * $P < 0.02$ by one-way ANOVA. Placebo infusions followed pretreatment with propantheline and methscopolamine administration preceded physostigmine infusions. Both pretreatments produced similar anticholinergic sensations, such as dry mouth, but methscopolamine caused a greater increase in heart rate.

we blocked peripheral muscarinic effects with either methscopolamine or propantheline. Equally potent doses of neostigmine, a cholinesterase inhibitor similar to physostigmine that does not cross the blood-brain barrier, did not change plasma epinephrine or norepinephrine levels. We previously reported that subjects receiving 0.022 mg/kg doses of physostigmine had increased heart rates and systolic and diastolic blood pressures, a finding that is replicated in the current study (13).

When epinephrine is infused at a rate of $2 \mu\text{g}/\text{min}$, it raises plasma epinephrine to levels similar to those seen in subjects in the current experiment who received high dose physostig-

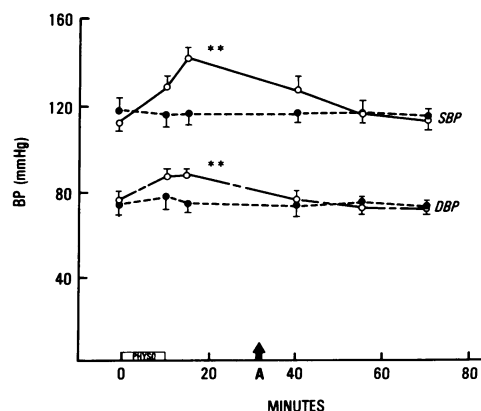


Figure 3. Systolic and diastolic blood pressure (SBP and DBP) after infusion of high dose (0.022 mg/kg) physostigmine (○) and placebo (●). Arrow indicates when atropine (0.8 mg) was given. * $P < 0.002$ by one-way ANOVA.

Table 1. Base Line Levels of Catecholamines, Blood Pressure, and Heart Rate and Changes Induced by Neostigmine at 10 Min Postinfusion

	E	NE	SBP	DBP	HR
	pg/ml	pg/ml	mmHg	mmHg	beats/min
Base line	39±5	426±100	117±3	79±2	103±2
Change	16±9	124±41	12.0±2.5	11.4±1.0	11.6±2.6

mine. The infused epinephrine produces all the cardiovascular effects we observed except for an increase in diastolic blood pressure (14). Our subjects were pretreated with noncentrally acting muscarinic blocking agents, which presumably prevent parasympathetic-mediated negative inotropic, chronotropic, and vasodilatory reflexes. We feel this may account for the slightly higher diastolic blood pressure increase that occurred in response to physostigmine-induced epinephrine release, compared with that seen in drug-free subjects who were infused with epinephrine. The small increase in norepinephrine blood levels that results from adrenomedullary catecholamine release probably contributes little in the way of cardiovascular effects, since norepinephrine is a less effective adrenergic agonist when injected into the venous circulation than when released by nerve endings adjacent to adrenergic receptors.

The sympathoadrenal system is anatomically and functionally organized to discharge diffusely (15). However, the adrenal medulla receives relatively more stimulation during anxiety (16), hypoglycemia (17), hypoxia (18), and acute ischemic injury (19) than do sympathetic nerve terminals. Since a feeling of anxiety accompanies high dose physostigmine administration (20), physostigmine may activate a central sympathoadrenal pathway that is stimulated during anxiety. Conversely, epinephrine may mediate some of the central effects of physostigmine. Exogenous epinephrine infusions increase anxiety and cause electroencephalographic desynchronization, and these effects appear to be direct central catecholaminergic effects, not the effect of changes in blood flow or blood pressure

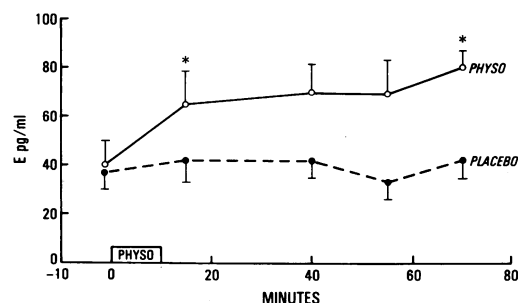


Figure 4. Plasma E concentration after low dose (0.4 mg) physostigmine infusion (○) and placebo infusion (●). The response to physostigmine is significant ($P < 0.05$) by ANOVA. * $P < 0.05$ by t test.

(21, 22). Physostigmine could cause anxiety both by direct central and epinephrine-mediated pathways. By analogy, anxiety can produce an epinephrine-mediated tachycardia. Perception of the tachycardia then worsens the anxiety.

Our results demonstrate that central cholinergic activation causes a selective stimulation of the adrenomedullary component of the sympathoadrenal system. This pathway may be important in the etiology of hypertension and other pathologic states. The spontaneously hypertensive rat has increased brain-stem acetylcholinesterase and cholinacetyltransferase (23, 24) and physostigmine causes a significantly greater increase in blood pressure in spontaneously hypertensive rats than in control animals (25, 26). Blockade of central acetylcholine with atropine, but not with peripherally acting methylatropine, decreases blood pressure in spontaneously hypertensive rats (27). Several studies in man report that epinephrine levels are elevated in human hypertensives (28, 29). We are currently investigating the cardiovascular and sympathoadrenal response to central cholinergic stimulation in human hypertensives.

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