Central Cardiovascular Effects of Physostigmine in Humans

David S. Janowsky, S. Craig Risch, and Leighton Y. Huey

SUMMARY Central cholinergic control of pulse rate and blood pressure has seldom been studied in humans. In the current study we contrasted the cardiovascular effects of the centrally acting cholinesterase inhibitor physostigmine, which increases central and peripheral acetylcholine levels, with those of saline placebo and of those of the non–centrally acting cholinesterase inhibitor neostigmine, which only increases peripheral acetylcholine levels. We found that physostigmine, in contrast to neostigmine and saline, caused significant and often profound increases in pulse rate and blood pressure levels in humans. Thus, we conclude that acetylcholine may have a role in central cardiovascular regulation in humans. We also found that administration of physostigmine may cause net increases in pulse of up to 74 beats/minute, systolic blood pressure increases of up to 50 mm Hg, and diastolic increases of up to 45 mm Hg. Such increases could be dangerous in elderly patients with concomitant cerebrovascular or coronary circulation disorders. (Hypertension 7: 140–145, 1985)

Key Words • hypertension • acetylcholine • cholinesterase inhibitors • physostigmine • neostigmine

CENTRALLY acting cholinomimetic agents have been used to treat symptoms of memory loss in Alzheimer’s disease as well as the manifestations of the central anticholinergic syndrome, which consist of disorientation, memory loss, and hallucinations and are caused by centrally acting anticholinergic agents. The use of acetylcholine precursors, physostigmine, and other directly and indirectly acting cholinomimetic agents has received increasing exposure in the lay press and in journal articles, and it is not impossible that oral or intravenous physostigmine may become widely used in the treatment of Alzheimer’s disease. Because Alzheimer patients tend to be elderly and may be prone to coronary and cerebral insufficiency as well as strokes and coronary occlusion, special consideration of the effects of any drug used on these patients’ cardiovascular systems is especially important.

Although several animal studies have suggested that central cholinergic mechanisms may be important in the regulation of blood pressure, only a few, largely anecdotal studies have explored the central effects of cholinomimetic agents on cardiovascular function in humans. Generally these reports have suggested that administration of or poisoning by centrally acting cholinesterase inhibitors increases blood pressure levels and pulse rates. This study is a controlled exploration in humans of the cardiovascular effects of the centrally acting, reversible cholinesterase inhibitor physostigmine.

Materials and Methods

The effects of physostigmine and saline placebo on pulse rate and blood pressure levels were compared in 62 men who were Veterans Administration psychiatric inpatients. The subject group was diagnosed by psychiatric classification into five groups, those with (1) a unipolar depressive disorder (n = 16), (2) a bipolar disorder (n = 13), (3) substance—alcohol, drug, or both—abuse (n = 12), (4) schizophrenia (n = 10), or (5) other disorders (n = 11). Median age was 31 years with a range of 20 to 53 years. Written informed consent was obtained from each subject in full accordance with the University of California, San Diego, and the San Diego Veterans Administration guidelines for human subjects. As described elsewhere, the study used a double-blind crossover design, and drugs were given in counterbalanced order. Each subject received, over a 10-minute period, physostigmine salicylate (0.022 mg/kg to a total of 2.0 mg) on one day and saline (placebo) 2 to 9
days before or 2 to 6 days after physostigmine administration. Atropine (up to 1.0 mg i.v.), given 20 minutes after the physostigmine infusion had ended, was used to abort the psychological and physiological effects of physostigmine, which include anergy, anxiety, depression, fatigue, and nausea and vomiting. To protect the subjects from the peripheral cholinergic effects of physostigmine (i.e., bradycardia, diarrhea, salivation), on each experimental day, each subject was given propantheline (45 mg, p.o., 90 minutes before physostigmine infusion) or methscopolamine (0.75 mg, i.m., 30 minutes before infusion). Propantheline was substituted when the methscopolamine supply became depleted. Propantheline was given to 37 patients and methscopolamine to 25.

To test whether the observed effects of physostigmine were due to a central or a peripheral mechanism, 15 other subjects received an intravenous infusion of the non–centrally acting cholinesterase inhibitor neostigmine (10 received a dose of 0.011 mg/kg, and 5 received a dose of 0.022 mg/kg) on one occasion and physostigmine (0.011 mg/kg no sooner than 2 days before or after neostigmine administration); again a double-blind crossover design was used. Twelve of these subjects received methscopolamine and 3 received propantheline as an anticholinergic pretreatment. These subjects were diagnostically subclassified into four groups: unipolar depressive disorder (n = 3), other bipolar disorder (n = 3), and normal (n = 2). The median age for this group of subjects was 31 years (age range, 23–51 years).

Subjects had their pulse rates taken and had sitting blood pressures measured with a standard sphygmomanometer on each experimental day, each subject. These subjects were diagnostically subclassified into four groups: unipolar depressive disorder (n = 3), other bipolar disorder (n = 3), and normal (n = 2). The median age for this group of subjects was 31 years (age range, 23–51 years).

As shown in Table 1, significant overall increases in pulse rate, systolic blood pressure, and diastolic blood pressure occurred after the administration of physostigmine in the 25 methscopolamine-pretreated subjects. Pulse rate and blood pressure were elevated before atropine infusion and rapidly decreased thereafter. Significant differences between physostigmine and placebo occurred 10 minutes after infusion for systolic blood pressure, at no specific times for diastolic blood pressure, and 0 and 10 minutes after infusion for pulse rate.

In addition, a wide range of net changes (the differences between postinfusion minus preinfusion placebo peaks subtracted from the differences between postinfusion minus preinfusion active drug peaks) in blood pressure and pulse rate after physostigmine administration in the 25 methscopolamine-pretreated subjects was noted. Net changes in pulse rate varied between −18 and +74 beats/minute, systolic blood pressure varied between −20 and +40 mm Hg, and diastolic

<table>
<thead>
<tr>
<th>Cardiovascular measures</th>
<th>Preinfusion period (minutes)</th>
<th>Postinfusion period (minutes)</th>
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<tbody>
<tr>
<td></td>
<td>−30</td>
<td>−1</td>
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<tr>
<td></td>
<td>+0</td>
<td>+10</td>
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<td></td>
<td>+30*</td>
<td>+45*</td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
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<tr>
<td>Physostigmine</td>
<td>120 ± 3 ± 13</td>
<td>121 ± 13 ± 0</td>
</tr>
<tr>
<td>Saline</td>
<td>119 ± 0 ± 12</td>
<td>122 ± 14 ± 14</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
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<tr>
<td>Physostigmine</td>
<td>78 ± 8 ± 10</td>
<td>81 ± 6 ± 8</td>
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<tr>
<td>Saline</td>
<td>78 ± 6 ± 8</td>
<td>84 ± 2 ± 10</td>
</tr>
<tr>
<td>Pulse (beats/min)</td>
<td>78 ± 6 ± 8</td>
<td>114 ± 7 ± 15</td>
</tr>
</tbody>
</table>

Data are means ± SD; p values represent significant treatment × time interactions, which include all preatropine time points.

*Postatropine time points, atropine given at +20 minutes.

fp < 0.01
blood pressure varied between −10 and +45 mm Hg.
The number of positive to negative net changes (not
counting subjects that did not change) was analyzed
with sign tests. For systolic blood pressure, although
14 subjects had positive net change scores and only 7
had negative net change scores (4 did not change), this
difference was not significant. The difference was
significant for diastolic blood pressure; 17 subjects
showed net increases and 6 showed net decreases (p <
0.05) The difference between the number of subjects
who showed positive pulse rate net changes compared
with those who showed negative changes (18 positive
versus 4 negative) was statistically significant (p <
0.01). Net changes in systolic blood pressure and pulse
rate are illustrated in Figure 1.

Similarly, in contrast to placebo infusion, physostigmine
administration caused statistically significant overall
increases in pulse rate, and systolic and diastolic
blood pressure in the 37 propantheline-pretreated
subjects, as shown in Table 2. Significant physostigmine
and placebo differences in systolic blood pressure
occurred 10 minutes after infusion. Significant
differences occurred 0 and 10 minutes postinfusion in
diastolic blood pressure and pulse rate. Net changes in
systolic blood pressure varied between −12 and +50
mm Hg. Net changes in diastolic blood pressure
ranged between −10 and +36 mm Hg. Net changes
in pulse rate varied between −6 and +54 beats/minute.
The proportion of positive to negative net changes
was statistically significant for systolic blood pressure
(26 positive and 9 negative, p < 0.01), diastolic blood
pressure (24 positive and 9 negative, p < 0.05), and
pulse rate (27 positive and 3 negative, p < 0.01), as
determined by sign tests. These changes in systolic
blood pressure and pulse rate are illustrated in
Figure 2.

![Figure 1](https://hyper.ahajournals.org/)

**Figure 1.** Net changes in pulse rate and systolic blood pressure in 25 methscopolamine-pretreated psychiatric patients. Net change equals maximum postplacebo values minus maximum prephysostigmine values minus maximum prephysostigmine values. Range of changes in pulse rate and systolic blood pressure are shown on abscissa.

<table>
<thead>
<tr>
<th>Table 2 Comparison of the Effects of Physostigmine and Saline in 37 Subjects Pretreated with Propantheline and Subsequently Treated with Atropine</th>
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</thead>
<tbody>
<tr>
<td><strong>Cardiovascular measures</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mm Hg)</strong></td>
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<tr>
<td>Physostigmine</td>
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<td>Saline</td>
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<td><strong>Diastolic blood pressure (mm Hg)</strong></td>
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<td>Physostigmine</td>
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<td><strong>Pulse (beats/min)</strong></td>
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<td>Physostigmine</td>
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Data presented are means ± SD. p values represent significant treatment x time interactions, which include all preatropine time points.
*Postatropine time points, atropine given at +20 minutes.
†p < 0.05
‡p < 0.01
§p < 0.001.
For the entire subject group (n = 62), the number of positive versus negative net changes in systolic and diastolic blood pressure and pulse rate was analyzed with sign tests. Forty subjects showed increases in systolic blood pressure and 16 showed decreases (p < 0.01); 41 showed increases and 15 showed decreases (p < 0.01) in diastolic blood pressure. For pulse rate, 45 showed increases and 7 showed decreases (p < 0.01).

Between-subject ANOVAs were performed on net change scores to assess diagnostic differences in reactions to physostigmine administration. None of the diagnostic groups differed significantly from each other with respect to cardiovascular reactions to physostigmine. Cardiovascular net change scores were correlated with nausea-emesis ratings, subject age, and net mood change scores. In the propantheline-pretreated subjects, 12 subjects showed no nausea, 13 became slightly nauseated, 4 became very nauseated, and 8 vomited after physostigmine administration. In the metoclopramide-pretreated subjects, 7 showed no nausea, 11 became slightly nauseated, 2 became very nauseated, and 5 vomited. For the subject group as a whole, no significant correlation between physostigmine-induced nausea and vomiting and physostigmine-induced net cardiovascular changes was noted. A significant increase in anxiety, behavioral inhibition, fatigue, confusion, and hostility was noted following physostigmine infusion. Some of these variables—anxiety, inhibition, fatigue—correlated weakly but significantly (r ≤ 0.367) with the physostigmine-induced net cardiovascular changes. No significant correlations between subject age and physostigmine-induced cardiovascular changes were noted.

When the effects of physostigmine and neostigmine administration were compared, significantly greater increases in pulse rate and systolic blood pressure were noted following physostigmine infusion. Neostigmine exerted a bradycardiac effect at the 0.022 mg/kg dose. Table 3 compares the effects of physostigmine and neostigmine administration.

**Discussion**

Central administration of acetylcholine, directly acting cholinergic agonists, or cholinesterase inhibitors has been shown to consistently increase blood pressure in a variety of conscious animals, including dogs, cats, and rats.\(^4,5\) Those directly acting muscarinic agonists that increase blood pressure include acetylcholine itself, carbachol, arecoline, and oxotremorine.\(^4,5\) Indirectly acting cholinomimetic agents, including the cholinesterase inhibitors physostigmine, neostigmine, and sarin, also have been shown to regularly and dramatically increase blood pressure in nonanesthetized animals.\(^7,12,17\) and cause a variable response in pulse rate, depending on the species studied. Conversely, but also indicative of cholinergic effects on the cardiovascular system, there are brain areas and situations, such as during anesthesia, in which administration of cholinergic agonists and cholinesterase inhibitors have been demonstrated to regularly induce hypotension.\(^14\)

Consistent with these animal studies, our data suggest that the centrally acting cholinomimetic agent physostigmine can significantly and in some cases dramatically increase pulse rate, and systolic and diastolic blood pressure in humans. We think that our 0- and 10-minute postphysostigmine time points represent the maximum time of increase in pulse rate and blood pressure, although pilot data indicate that some subjects peak at 5 minutes after termination of physostigmine infusion. This observation contrasts with the peripheral effects of muscarinic and mixed cholinomimetic agents, which generally decrease pulse rate and blood pressure. Because pulse rate and systolic blood pressure significantly increased after physostigmine infusion but not after non-centrally acting neostigmine infusion, the enhancing effects of physostigmine on blood pressure and pulse rate are likely to be of central origin. As atropine appears to have reversed these increases in blood pressure and pulse rate, these effects probably are due to stimulation of central muscarinic receptors. Because at least partial vagal blockade was
achieved, the increases in pulse rate and blood pressure might have been blocked or antagonized had methscopolamine been used. Data from cholinesterase overdoses suggest, however, that these toxic agents often increase blood pressure and pulse rate.18

The hypertensive effect of acetylcholine appears ultimately to involve peripheral sympathetic nerve terminals at the end-organ level19-27 and does not involve the release of adrenal catecholamines,22 24 although such release does occur with central mescarinic stimulation. Ablation studies have shown that bilateral vagotomy does not block the hypertensive effects of cholinomimetics, as does pithing or ablation of the spinal cord rostral to the sympathetic outflow. Furthermore, sympathetic efferent neuronal activity has been shown to be enhanced following central mescarinic stimulation.19 24

A number of studies have shown that drugs that block the peripheral sympathetic nervous system cause significant attenuation of the cholinomimetic-induced pressor response, and conversely, administration of drugs that enhance peripheral sympathetic activity enhance the pressor response to cholinomimetics.25-27

A logical extension of these observations would suggest that central cholinergic pathways may contribute to the causation of certain forms of hypertension, possibly through increasing sympathetic outflow. Indeed, there is considerable evidence from animal experiments to support this possibility.18 28-32 It has been observed that the hypertensive response to physostigmine is exaggerated in spontaneously hypertensive rats, and that this effect occurs even in the prehypertensive rat, as well as in older animals with established hypertension. Thus, it is possible that cholinergic mechanisms may be important in the causation of pathological hypertension as well as in the regulation of increases in blood pressure of sympathetic origin.

Our study also demonstrated temporary physostigmine-induced increases in net pulse rates of up to 74 beats/minute and increases in systolic blood pressure of up to 50 mm Hg over postanticholinergic baseline values. Our subjects were relatively young (not older than 55 years) and had been carefully screened not to include those with cardiovascular disease. Although we noted absolutely no sequela from our experimental procedure, we believe that such rapid and high increases in pulse rate and blood pressure could have potentially serious deleterious effects in an elderly population. Therefore, because the use of physostigmine is increasing as a treatment for Alzheimer's disease, we would recommend careful screening and monitoring of patient cardiovascular status in elderly patients given physostigmine.

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TABLE 3 Comparison of the Effects on Blood Pressure and Pulse Rate in 15 Subjects Pretreated with Physostigmine (0.011 mg/kg, n = 10) and Neostigmine (0.022 mg/kg, n = 5)

<table>
<thead>
<tr>
<th>Cardiovascular measures</th>
<th>Preinfusion period (minutes)</th>
<th>+0</th>
<th>+10</th>
<th>+30*</th>
<th>+45*</th>
<th>+60*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>-30</td>
<td>-1</td>
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</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>Physostigmine</td>
<td>113 6±9.4</td>
<td>115 3±12.9</td>
<td>122 1±9.6</td>
<td>125 5±10.9</td>
<td>119 9±10.2</td>
</tr>
<tr>
<td></td>
<td>Neostigmine</td>
<td>119 2±9.0</td>
<td>114 3±12.9</td>
<td>115 3±13.6</td>
<td>116 1±13.2</td>
<td>115 2±12.7</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>Physostigmine</td>
<td>73 3±8.1</td>
<td>76 3±8.1</td>
<td>80 3±7.8</td>
<td>82 6±11.2</td>
<td>79 5±7.8</td>
</tr>
<tr>
<td></td>
<td>Neostigmine</td>
<td>73 9±9.1</td>
<td>75 5±10.9</td>
<td>78 1±12.4</td>
<td>77 3±12.2</td>
<td>76 3±11.0</td>
</tr>
<tr>
<td>Pulse (beats/min)</td>
<td>Physostigmine</td>
<td>73 2±6.8</td>
<td>101 1±14.9</td>
<td>108 0±14.4</td>
<td>118 7±19.9</td>
<td>106 8±18.8</td>
</tr>
<tr>
<td></td>
<td>Neostigmine</td>
<td>73 2±9.2</td>
<td>101 9±11.8</td>
<td>100 1±11.8</td>
<td>92 8±15.5</td>
<td>88 1±13.9</td>
</tr>
</tbody>
</table>

Data presented are means ± SD, p values represent significant treatment×time interactions, which include all preatropine time points.
*Postatropine time points, atropine given at +20 minutes
†p < 0.01
‡p < 0.001
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