Effects of Antihistaminic Drugs on the
Cardiac Responses to Sympathetic
Nerve Stimulation

Yasuo Matsuda
Department of 2nd Internal Medicine, Yamaguchi
University School of Medicine Ube, Yamaguchi,
Japan
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ABSTRACT

In open-chest, anesthetized dogs, the effects of blocking the neurona uptake mechanisms for norepinephrine (NE) were studied on the inotropic and chronotropic responses to cardiac sympathetic nerve stimulation. Cocaine (COC), a standard neuronal uptake blocking agent, did not significantly potentiate the inotropic and chronotropic responses, but did prolong them. The antihistaminic drugs, chlorpheniramine (CHL) and tripelennamine (TRI), which are also potent neuronal uptake blocking agents, only slightly potentiated the inotropic responses at the lower stimulation frequencies, but did not significantly potentiate the chronotropic responses. However, the inotropic and chronotropic responses were significantly prolonged after either of these antihistaminic drugs had been given. It is suggested that the absence of appreciable potentiation of the inotropic and chronotropic responses to sympathetic neural stimulation in vivo is not a property peculiar to specific neuronal uptake blocking drugs, such as COC and desipramine (DMI), but is probably a general characteristic of such agents.

Key Words: cocaine; chlorpheniramine; tripelennamine
neuronal uptake

In the heart, neuronal uptake of the released norepinephrine (NE) at postganglionic sympathetic nerve terminals appears to be one of the principal mechanisms for terminating the effects of sympathetic neural activity11. Cocaine (COC) and desipramine (desmethyllumipramine, or DMI) are probably the two most efficacious and widely used blocking agents for the neuronal uptake of NE. In isolated preparations of cardiac tissue, it was observed that COC and DMI potentiated and prolonged the cardiac responses to both exogenous and neurally released NE2-9.
Although similar effects of uptake blockade on the cardiac responses to neurally released NE have sometimes been observed in more intact preparations\textsuperscript{10-12}, in most cases the results have been contradictory. In several studies carried out in open-chest dogs, the cardiac responses to sympathetic stimulation were not potentiated by these neuronal uptake blocking agents, although the responses were prolonged significantly\textsuperscript{13-16}. On the other hand, it has been amply demonstrated that COC and DMI do potentiate and prolong the cardiac responses to exogenous NE in intact animals\textsuperscript{15,16,17-19}, just as in isolated tissues.

Certain antihistaminic drugs are also known to be potent inhibitors of the neuronal uptake of NE\textsuperscript{15,20-22}. We decided to compare the effects of COC with those of the antihistaminic drugs, chlorpheniramine (CHL) and tripelemamine (TRI), under identical experimental conditions, in order to determine whether the absence of potentiation of cardiac responses in vivo is a general characteristic of neuronal uptake blockers, or whether only certain agents, notably COC and DMI, fail to potentiate the cardiac responses to sympathetic nerve stimulation.

METHODS

Experiments were conducted on 25 mongrel dogs with a mean weight of 19.7 ± 5.2 (SD) kg. The animals were anesthetized with sodium pentobarbital, 30 mg/kg iv. A tracheal cannula was inserted through a midline cervical incision and intermittent positive pressure ventilation was begun. Both vagi were crushed at the mid-cervical level by tight ligatures. The chest was opened through a transverse incision in the fourth intercostal space. The upper poles of both stellate ganglia were crushed by tight ligatures, in order to interrupt almost all of the tonic sympathetic neural activity to the heart\textsuperscript{23}.

Arterial blood pressure was measured from a femoral artery by means of a Statham transducer (P 23AA). A Walton-Brodie strain gauge arch was used to measure the myocardial contractile force. It was attached to the right ventricle, parallel and about 1 cm lateral to the anterior descending coronary artery, at a site about halfway between the apex and base of the heart. Cardiac cycle length was derived electronically from the strain gauge arch output. Arterial blood pressure, right ventricular contractile force and cardiac cycle length were recorded on a direct-writing Brush oscillograph (Mark 260).

Each animal was assigned randomly to one of the following groups; (1) a control group (n=5), (2) a group that received cocaine (n=7), (3) a group that received chlorpheniramine (n=7), and (4) a group that received tripelemamine (n=6). Each experiment was divided into two
periods. During the first period, no uptake blocking drug was given. Shielded iridium electrodes (Harvard Apparatus Co.) were applied to both limbs of the right ansa subclavia. The decentralized right ansa subclavia was stimulated at frequencies of 0.5, 1, 2, 4, and 8 Hz. The order of applying these frequencies was randomized. Each stimulation consisted of a 60 sec train of square wave pulses (Grass stimulator, model S9). Each pulse was 2 ms in duration, and of supramaximal voltage (usually 15 v).

After the contractile force, cycle length, and arterial blood pressure responses to the various frequencies of stimulation were determined, the appropriate uptake blocking drugs were given to the animals in groups 2, 3 and 4. The animals in group 1 served as controls. In group 2, cocaine hydrochloride (COC) was infused intravenously at a rate of 330 μg/kg/min for a 15-min period, and then at a rate of 66 μg/kg/min for the remainder of the experiment. Five min after this change in the rate of infusion, the cardiac responses to ansal stimulation were determined over the same range of stimulation frequencies cited above; the order was again randomized. In group 3, chlorpheniramne (CHL) was given intravenously at a rate of 0.5 mg/kg/min for a 20 min period and in group 4, tripeplennamine (TRI) was infused intravenously at a rate of 0.5 mg/kg/min for a 20 min period. After these infusions were completed, the cardiac responses to ansal stimulation were measured at the various stimulation frequencies cited above.

RESULTS

Figure 1 shows the changes in right ventricular contractile force, cardiac cycle length, and arterial blood pressure elicited by stimulation of the right ansa subclavia in a representative experiment. The record was obtained during the first experimental period, prior to the administration of an uptake blocking drug. Ansal stimulation (between the arrows) evoked a 230 per cent increase in contractile force, a 225 ms reduction in cardiac cycle length, and a triphasic change in arterial blood pressure. The “durations” of the cardiac responses after cessation of stimulation were assessed on the basis of the 50 per cent recovery time, which is defined as the time required to return halfway from the level attained at the end of stimulation back to the steady-state, poststimulation level. The durations were 30 s and 28 s for contractile force and cardiac cycle length, respectively.

After period 1 had been completed, COC, CHL, or TRI infusions were given to the animals in the appropriate group. The animals in the control group did not receive one of these drugs. The composite data
Figure 1 The changes in cardiac cycle length, contractile force and arterial blood pressure produced by a 1 min train of supramaximal stimuli (15 V, 2 ms, 4 Hz) to the decentralized right ansa subclavia in a representative experiment. The arrows denote the beginning and end of the stimulation period. The time marker indicates 1 min intervals.

for each group are shown in Figures 2 and 3. The mean data are represented by the symbols in the figures. Second degree polynomial regression equations were fitted to these data, and the continuous and dashed curves in the figures are the graphs of the equations for the data obtained before and after the uptake blocking drug, respectively. In the control and COC groups, the magnitudes of the contractile force responses in the second experimental period were not appreciably different from those in the first period (upper panels of Fig. 2). However, ansal stimulation did elicit a greater contractile force response after CHLt than before CHL; the differences were significant at the three lower stimulation frequencies (0.5, 1 and 2 Hz; P ≤ 0.025). When these
Figure 2 The changes in the magnitude and duration of the myocardial contractile force responses to supramaximal stimulation of the right ansa subclavia, at frequencies from 0.5 to 8.0 Hz. The continuous curves represent the second degree polynomial regression equations which were fit to the mean data for the first experimental period (closed symbols, prior to the administration of any neuronal uptake blocking drugs. The dashed curves were fit to the mean data (open symbols), for the second experimental period; during this period, the ansa subclavia was stimulated in the absence of neuronal uptake blockade (control group) or after the administration of cocaine, chlorpheniramine, or tripelemamine. R₁ and R₂ are the non-linear correlation coefficients for the curves in the first and second experimental periods, respectively.
Figure 3  The changes in the magnitude and duration of the cardiac cycle length responses to supramaximal stimulation of the right ansa subclavia, at frequencies from 0.5 to 8.0 Hz. The continuous curves represent the second degree polynomial regression equations which were fit to the mean data for the first experimental period (closed symbols), prior to the administration of any neuronal uptake blocking drugs. The dashed curves were fit to the mean data (open symbols) for the second experimental period; during this period, the ansa subclavia was stimulated in the absence of neuronal uptake blockade (control group) or after the administration of cocaine, chlorpheniramine or tripelemamine. $R_1$ and $R_2$ are the non-linear correlation coefficients for the curves in the first and second experimental periods, respectively.
differences were compared with the differences between the responses in periods 1 and 2 in the control group, the differences were significant at the same stimulation frequencies (P≤0.025). Similarly, the contractile force responses were significantly greater after TRI at the two lower stimulation frequencies (0.5 and 1 Hz; P≤0.025). The increments in contractile force at these stimulation frequencies were also significantly different from those in the control group (P≤0.025).

In the control group, there were no appreciable differences in the duration of the contractile force response between the first and second experimental periods (lower panels of Fig. 2). After COC, the duration of the contractile force response was significantly prolonged at all stimulation frequencies (P≤0.025). These prolongations were also significantly different from those in the control group (P≤0.05). CHL also provoked considerable prolongations of the contractile force responses to anal stimulation which were significant (P≤0.05) at all stimulation frequencies except 8 Hz. These prolongations after CHL were significantly different from those in the control group at stimulation frequencies of 0.5, 1 and 2 Hz (P≤0.05). There were no significant differences between the prolongations of contractile force responses after COC and those after CHL. After TRI, the contractile force responses were markedly prolonged at all stimulation frequencies (P≤0.01). The prolongations after TRI were significantly greater than those in any of the other group (P≤0.05).

In the control group, the magnitudes of the cardiac cycle length responses during the second experimental period were slightly less than those during the first period (upper panels of Fig. 3), but the differences were not significant. After COC, the changes in the cycle length magnitudes were not significantly different from those in the control group. The magnitudes of the cycle length responses were only slightly different after CHL than before CHL, but these small differences were significant statistically (P≤0.05) at the two lowest stimulation frequencies (0.5 and 1 Hz). Similarly, the magnitudes of the cycle length responses were not much different before and after TRI, except at the highest stimulation frequency (8 Hz). At that frequency, the response was smaller after TRI than before (P=0.025, control vs TRI groups).

In the control group, there were no appreciable differences in the durations of the cardiac cycle length responses between the first and second experimental periods (lower panels of Fig. 3). After COC, CHL and TRI, the durations of the cycle length responses were markedly prolonged, and significantly different from those of the control group at all stimulation frequencies (P<0.0005). The prolongations after CHL
were not significantly different from those after COC. However, the prolongations after TRI were significantly greater than those after COC at the stimulation frequencies of 0.5, 1 and 4 Hz (P \leq 0.05) and greater than those after CHL at all stimulation frequencies (P \leq 0.025).

DISCUSSION

Cocaine (COC) and desipramine (DMI) are presently the most effective blockers of the neuronal uptake of norepinephrine (NE). Hence they have been widely used to assess the role of neuronal uptake in the sympathetic neural regulation of cardiac function. In several studies in open-chest dogs, the cardiac responses to sympathetic stimulation were not potentiated by either COC or DMI, although these responses were prolonged significantly\(^{13-16}\). Our present data (Figs. 2 and 3) from the group that received COC confirm these previous results.

Certain antihistaminic drugs are also known to be potent inhibitors of the neuronal uptake of NE\(^{13,20-22}\). In the denervated heart of the cat, the antihistaminic drugs, antazoline, chlorcyclizine, promethazine, mepyramine and diphenhydramine have been reported to potentiate the cardiac responses to exogenous NE\(^{20}\). It has been observed that, in isolated rat atria, tripelemamine (TRI), diphenhydramine and chlorpheniramine (CHL) potentiated the chronotropic responses to exogenous NE\(^{21}\), just as COC and DMI do in isolated cardiac tissues. In the open-chest dog, TRI and CHL potentiated the inotropic and chronotropic responses to exogenous NE\(^{13}\). However, they did not potentiate the chronotropic responses to sympathetic nerve stimulation, although they did prolong them significantly\(^{13}\). In that study, the sympathetic nerves were stimulated at supramaximal frequencies for only 15 sec. Only 2 experiments were performed at submaximal stimulation frequencies with each drug, and the results were similar directionally to those in the experiments in which supramaximal stimulation frequencies were used. The inotropic responses to sympathetic stimulation were not studied.

Our present data show that CHL and TRI produced a small, but significant, potentiation of the contractile force responses to sympathetic stimulation (upper panels of Fig. 2), but only at the lower stimulation frequencies. The cardiac cycle length responses were not appreciably potentiated (upper panels of Fig. 3). However, the durations of the contractile force responses (lower panels of Fig. 2) were significantly prolonged by TRI at all stimulation frequencies, and by CHL at the lower stimulation frequencies. Furthermore, the cardiac cycle length responses were markedly prolonged by both drugs at all stimulation frequencies (lower panels of Fig. 3). The cardiac cycle length responses
were more prolonged than were the contractile force responses, and the effects were comparable to those produced by COC.

The absence of potentiation of the cardiac responses has been noted and explained by invoking some side action, such as a local anesthetic effect of these neuronal uptake blocking drugs\textsuperscript{22, 24}. In the group that received COC, the absence of the potentiation might be explained on the basis of this anesthetic action. However, some studies in vitro have demonstrated that potentiation by the neuronal uptake blocking drugs occurs mainly at the lower stimulation frequencies\textsuperscript{2, 40}. The slight potentiation of the contractile force responses at the lower stimulation frequencies in the groups that received CHL and TRI in our study are consistent with these earlier studies. At the lower stimulation frequencies, a greater fraction of the liberated NE may ordinarily be taken up by the nerve terminals. Therefore, uptake blockade might be more likely to potentiate the cardiac responses at these low frequencies\textsuperscript{40}. However, the influences of COC and DMI were similar to those of the antihistaminic drugs, CHL and TRI, on the responses to sympathetic stimulation. This suggests that the absence of appreciable potentiation of the inotropic and chronotropic responses to sympathetic stimulation in vivo is a general characteristic of the neuronal uptake blocking agents, rather than a side-effect of certain blocking agents.

The prolongations of the cardiac cycle length responses are greater than those of the contractile force responses in this and other studies\textsuperscript{14, 15}. The neurally released NE is dissipated by two principal mechanisms: (a) diffusion into the blood stream, and (b) tissue re-uptake\textsuperscript{25}. In the presence of effective blockade of neuronal uptake, the principal mechanism for disposing of the neurally released NE must be by diffusion away from the site of release and into the coronary blood stream. It is well known that myocardial blood flow increases considerably during cardiac sympathetic activity\textsuperscript{15, 26}. The augmented flow is ascribable largely to the associated increase in cardiac work and energy utilization\textsuperscript{26}. Therefore, the greater prolongation of the chronotropic than of the inotropic responses to sympathetic nerve stimulation might be produced by a less effective washout of the neurally released NE by the blood circulation in the pacemaker tissue than in the myocardium. Koerker and Moran\textsuperscript{14} proposed that increased sympathetic activity might cause a direct vasoconstriction of the vessels to the sinoatrial node, but an indirect vasodilation of the vessels to the vigorously contracting myocardium, by virtue of the increased metabolism. These oppositely directed changes in coronary vascular resistance could account for the greater prolongation of the chronotropic than of the inotropic responses
to sympathetic nerve stimulation after neuronal uptake blockade. However, data are not yet available concerning the changes in blood flow to the region of the sinoatrial node under conditions of increased sympathetic activity and neuronal uptake blockade.

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