

Cardiovascular effects of nicotine, chlorisondamine, and mecamylamine in the pigeon

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Abstract

Chlorisondamine and mecamlamine are nicotinic antagonists that produce both ganglionic and central blockade. Chlorisondamine, when administered as a large systemic dose, produces a persistent central block, despite being charged. The present study evaluated the cardiovascular effects of chlorisondamine. Shortly after administration, chlorisondamine (0.10, 1 and 10 mg/kg, intramuscular, im) lowered blood pressure significantly and decreased heart rate at the low dose (0.1 mg/kg, im) and increased heart rate at the high dose (10 mg/kg, im). Mecamlamine (1 and 10 mg/kg, im) also lowered blood pressure and heart rate. Following both antagonists, heart rate returned to baseline values within 90 minutes and blood pressure within 24 hours.

Low doses of nicotine (0.01 - 0.03 mg/kg, im) lowered blood pressure, but did not affect heart rate. Higher doses (0.10 to 3.2 mg/kg, im) transiently increased blood pressure and heart rate. Subsequent to antagonist administration, nicotine was administered to determine if either drug blocked the cardiovascular effects of nicotine. Chlorisondamine (0.1, 1, and 10 mg/kg, im) administered 30 minutes prior to nicotine, blocked the increases blood pressure and heart rate. Only the high dose (10 mg/kg, im) of chlorisondamine administered 24 h before nicotine produced a blockade of nicotine's pressor effect. This block diminished within 3 days. Mecamlamine (1 mg/kg, im) antagonized only nicotine's tachycardic effect. Longer pretreatment with mecamlamine (10 mg/kg, 24 h prior to nicotine challenge) did not antagonize the cardiovascular effects of nicotine. Thus, chlorisondamine produces a longer lasting blockade of nicotine's cardiovascular effects than mecamlamine.

Chlorisondamine and mecamlamine are antagonists of nicotinic acetylcholine receptors in the autonomic ganglia. Blockade of ganglionic nicotinic acetylcholine receptors attenuates sympathetic input to arteries causing vasodilation and a decrease in blood pressure. Ganglionic blocking drugs were used to treat hypertension but their use was limited by side effects such as: dizziness, fatigue, pupil dilation, dryness of mouth, visual impairments, and orthostatic hypotension (Darvill, 1957; Anonymous, 1962; Smirk and Hamilton, 1956). The purpose of this study is to evaluate the cardiovascular effects of chlorisondamine in order to compare its peripheral and central nicotinic blockade in pigeons.

Chlorisondamine is a charged molecule that does not penetrate the blood brain barrier readily. Therefore, blockade of central nicotinic effects is not apparent until 24 h after administration, while autonomic blockade occurs rapidly. A systemic dose of 10 mg/kg chlorisondamine is necessary to achieve persistent central blockade in rats (Clarke et al, 1984; El-Bizri et al., 1994; Decker et al., 1994a,b; Reuben et al., 1998; Clarke and Reuben, 1996), however a 10 – 100 fold lower dose will block nicotinic acetylcholine receptors in the autonomic ganglia. The central blockade endures up to one week in the pigeon (Chadman and Woods, 2001) and 3-12 weeks in rodents (Clarke et al, 1984; El-Bizri et al., 1994; Decker et al., 1994a,b; Reuben et al., 1998; Clarke and Reuben, 1996).

Blockade of central nicotinic receptors may help in smoking cessation therapy by blocking the positive reinforcing effects of nicotine thereby dissociating them from the action of smoking. Central blockade of nicotinic receptors by chlorisondamine has been characterized most fully in the rat. An intraperitoneal (i.p.) injection of 10 mg/kg chlorisondamine attenuates the nicotine-induced increases in locomotor activity for up to five weeks (Clarke et al, 1984;

Decker et al., 1994a,b) and blocks ex-vivo nicotine-induced release of [³H]-dopamine (El-Bizri et al., 1994) or [³H]-norepinephrine from synaptosomes for up to 12 weeks (Reuben et al., 1998; Clarke and Reuben, 1996). In the pigeon, chlorisondamine (7.5 mg/kg, intramuscular, i.m.) antagonizes decreases in rate for food-reinforced pecking caused by nicotine for up 4 days (Chadman and Woods, 2001).

The systemic dose of chlorisondamine necessary for persistent central nicotinic blockade appears to be 10 fold higher than the dose needed for ganglionic blockade. The effects of high doses of chlorisondamine on physiological functions controlled by the autonomic ganglia, however, remain to be fully explored. In conscious rats and squirrel monkeys, chlorisondamine (5 mg/kg intravenously, i.v.) causes marked hypotension and bradycardia (Abdel-Rahman, 1989; Tella et al., 1993; Santajuliana et al., 1996). The hypotensive effect rapidly reaches its peak within 5 min, while the effect on heart rate requires 30 min to produce maximal bradycardia (Santajuliana et al., 1996). In rats, 20 mg/kg chlorisondamine is toxic, causing severe respiratory distress (Tella et al., 1992).

Mecamylamine is a non-competitive antagonist of nicotinic acetylcholine receptors that blocks the channel of the nicotinic receptor similar to chlorisondamine (Varanda et al., 1985; Wang et al., 1997). The nicotinic antagonist mecamylamine blocks nicotine actions in both autonomic ganglia and the central nervous system. It is approved for the treatment of hypertension and is in clinical trial for smoking cessation (Shytle et al., 2002). The environmental cues reinforced by smoking may be attenuated by mecamylamine administration prior to smoking cessation (Rose et al., 1998). Mecamylamine also facilitates long-term abstinence from smoking when added to nicotine patch treatment (Rose et al., 1994, 1998).

Nicotine has behavioral effects in the pigeon that are blocked by chlorisondamine and mecamylamine (Chadman and Woods, 2001). The pecking behavior of pigeons is easily trained and maintained and useful for studying drug effects on operant behavior. However, the cardiovascular effects of these drugs in the pigeon have not been documented. In humans, smoking or intravenous nicotine usually elicits a 5-10 mm Hg increase in blood pressure and a 15-25 beat per minute increase in heart rate within 5 min (reviewed in Robertson et al., 1988).

These experiments examined the ganglionic blockade of high doses of chlorisondamine utilizing changes in heart rate and blood pressure. Blood pressure and heart rate were compared among several doses of chlorisondamine and mecamylamine to evaluate the degree of ganglionic blockade. The duration of chlorisondamine's ganglionic blockade was assessed by administering chlorisondamine or mecamylamine either 30 min, 24 h, or 3 days before nicotinic-induced stimulation of blood pressure and heart rate.

Methods

Subjects: White Carneaux pigeons, housed individually, were used for these experiments. The pigeons were between 450-630 g, housed singly with a 12 hour light/dark schedule. The pigeons had food, water, and grit freely available. Studies were performed in accordance with the Guide for the Use and Care of Laboratory Animals as adopted and promulgated by the National Institutes for Health. The experimental protocols were approved by the University of Michigan University Committee for the Use and Care of Animals.

Surgery: The pigeons were hooded and restrained. The area surrounding the brachial artery was anesthetized with lidocaine and swabbed with disinfectant. The brachial artery was exposed and a catheter inserted. The area was then sutured and the catheter plugged.

Cardiovascular Testing: The arterial catheter was connected to a pressure transducer coupled to a Grass polygraph; data were recorded using Polyview software, Astro-Med (West Warrick, RI). Pigeons were allowed to habituate for 20 min at the beginning of the session. Then a saline intramuscular injection was administered and blood pressure and heart rate recorded for 10 min. After that period either a ganglionic blocking drug was administered and recorded alone and/or followed by nicotine injections spaced 20 min apart. All injections were administered intramuscularly. The first group of experiments compares the effects of three doses of chlorisondamine (0.1, 1, and 10 mg/kg) and two doses of mecamylamine (1 and 10 mg/kg) for 2 h on blood pressure and heart rate in the pigeon. The next set of experiments evaluates increasing doses of nicotine (0.01 to 3.2 mg/kg) on blood pressure and heart rate and after pretreatment with chlorisondamine (0.1, 1, or 10 mg/kg); mecamylamine (1 or 10 mg/kg); or vehicle 30 min or 24 h before the nicotine doses to ascertain if the effects of chlorisondamine on blood pressure and heart rate can be overcome by nicotine.

Data Analysis: Heart rate and blood pressure were averaged over 10 sec from each min for each recording. In the groups administered one dose of chlorisondamine or mecamylamine, the baseline blood pressure and heart rate values from each subject were subtracted out and the data presented as change from the saline baseline. A one-way ANOVA with Tukey's Multiple Comparison posttest was used to compare the groups. The data from the groups pretreated with chlorisondamine or mecamylamine followed by nicotine were divided by the time-matched values from the saline group and presented as % saline. The peak values subsequent to each injection were analyzed comparing the groups using two-way ANOVA with Bonferroni's posttests.

Materials: Chlorisondamine diiodide was purchased from Tocris (Ellisville, MO).

Mecamylamine, nicotine base, and lidocaine were purchased from Sigma (St. Louis, MO). The drugs were dissolved in sterile water or saline.

Results

The first set of experiments measured the change in heart rate and blood pressure over a several chlorisondamine (0.1 to 10 mg/kg) and mecamylamine (1 to 10 mg/kg) doses. A single injection of saline lead to a gradual ~ 5mm Hg decrease in blood pressure, from 130 mm Hg to 125 mm Hg over the course of the recording session (Fig. 1A change from baseline). Heart rate of pigeons varied around 175 beats per minute over the recording session after a single saline injection (Fig. 1B change from baseline).

Chlorisondamine and Mecamylamine Treatment

Chlorisondamine (0.10, 1, & 10 mg/kg) lowered blood pressure significantly ($p < 0.001$) compared to saline (Fig. 1A). The decrease in blood pressure following 0.1 mg/kg chlorisondamine was not as long lasting as the higher doses and returned close to baseline levels by 75 min. The depressor effect (10-15 mm Hg decrease) of the larger doses of chlorisondamine (1 and 10 mg/kg) had a faster onset and lasted for the remainder of the recording session (2 h); but it returned to baseline values at 24 h (data not shown).

Chlorisondamine caused a biphasic, dose-dependent response in heart rate (Fig. 1B). The lowest dose of chlorisondamine, 0.1 mg/kg, lowered heart rate ($p < 0.001$), 1 mg/kg had no effect and 10 mg/kg increased heart rate ($p < 0.001$). Following 0.10 mg/kg chlorisondamine, heart rate lowered rapidly and returned to control group levels within 35 minutes (Fig. 1B). Chlorisondamine, 10 mg/kg, reached the peak increase in heart rate at 10 minutes and gradually returned to similar levels as the control group after 75 minutes (Fig. 1B).

The changes in heart rate did not follow the same time course as the decrease in blood pressure. Chlorisondamine, 0.1 mg/kg, lowered both blood pressure and heart rate, but the higher dose (10 mg/kg) lowered blood pressure and increased heart rate. Chlorisondamine, 1

mg/kg, lowered blood pressure within 20 min and maintained its decrease for the entire session but caused no change in heart rate. Chlorisondamine (10 mg/kg) took 30 min to achieve the maximum depressor effect and maintained the decrease for the entire session while the increase in heart rate peaked within 10 min and was gone in 75 min.

Mecamylamine significantly lowered both blood pressure ($p < 0.001$; Fig. 1C) and heart rate ($p < 0.001$; Fig. 1D).

Nicotine

Nicotine was administered in increasing doses from 0.01 to 3.2 mg/kg at 20 minute intervals. Twenty minute intervals were chosen because nicotine is a fast acting drug and this allowed time for blood pressure and heart rate to return to baseline values between injections. As a control, saline injections were administered at the same time intervals. During the repeated saline injections blood pressure gradually decreased by 20 mm Hg (Fig. 2A) with small increases following each injection. This decrease in blood pressure was larger than observed after a single saline injection (Fig. 1A). Heart rate was relatively stable between 175 - 200 beats per minute (Fig. 2B) over the session, which was slightly higher than the heart rate after a single saline injection (Fig. 1B). The peak heart rate and blood pressure after each saline injection did not differ greatly among the saline injections and were used as the 100% baseline (Fig. 2A,B insets).

There was no change in blood pressure or heart rate at low doses of nicotine (0.01 and 0.032 mg/kg). As the nicotine dose increased from 0.10 – 3.2 mg/kg, nicotine immediately caused a transient increase in blood pressure and heart rate (Fig. 2A, B), with the increase reaching a maximum at 0.10 mg/kg nicotine. The increase in blood pressure had a longer duration as the dose increased, but after the highest dose (3.2 mg/kg) there was a fast drop in

blood pressure after the peak increase. However, blood pressure did not fall as low as the values from the subjects in the repeated saline injection group.

Nicotine – Antagonist Interactions: Blood Pressure

Chlorisondamine (0.10 mg/kg) 30 min prior to nicotine significantly ($p < 0.05$) attenuated the peak pressor effects of nicotine (Fig. 3A). When this dose of chlorisondamine was administered 24 h before the nicotine doses there was no blockade of nicotine-induced increases in blood pressure, and there was a slight, non-significant, enhancement of the peak effects of nicotine (Fig. 3A).

The 30 min pretreatment of chlorisondamine (1mg/kg) significantly ($p < 0.001$) antagonized the nicotine-induced increases in blood pressure (Fig. 3B). With 24 h pretreatment of 1 mg/kg chlorisondamine, the pressor effect of the lowest doses of nicotine (0.01- 0.032 mg/kg) was enhanced similarly to that observed with 24 h pretreatment with 0.1 mg/kg chlorisondamine (Fig. 3A).

The largest dose of chlorisondamine, 10 mg/kg, significantly attenuated the increases in blood pressure caused by nicotine with both 30 min ($p < 0.001$) and 24 h ($p < 0.001$) pretreatment (Fig. 4C). However, the blockade was no longer evident by 3 days and at that time there was an enhancement of the pressor effect of the lowest two doses of nicotine. This enhancement was similar to, but more pronounced, than that observed with 24 h pretreatment with 0.1 and 1 mg/kg chlorisondamine.

A 30 min pretreatment of 1 mg/kg mecamylamine did not attenuate the nicotine-induced increases in blood pressure (Fig. 3D). Twenty-four hour pretreatment with 10 mg/kg mecamylamine did not significantly block nicotine's pressor effect (Fig. 3D). However, there was a significant ($p < 0.01$) difference in the peak blood pressure following nicotine doses

between 30 min pretreatment of 1 mg/kg mecamylamine and 24 h pretreatment of 10 mg/kg. The 30 min pretreatment of 1 mg/kg mecamylamine blocked the pressor effect of nicotine, while 10 mg/kg mecamylamine at 24 h was similar to the lower doses of chlorisondamine and had a trend towards enhancing the pressor effect of nicotine.

Nicotine – Antagonist Interactions: Heart Rate

Chlorisondamine (0.10 mg/kg), regardless of length of pretreatment had no significant effect on nicotine-induced increases in heart rate (Fig. 4A). The 30 min pretreatment of chlorisondamine significantly ($p < 0.05$) increased the peak effect of 0.032 mg/kg nicotine only, the opposite of the decrease in heart rate observed after 0.10 mg/kg chlorisondamine alone (Fig. 2B). Chlorisondamine (1 mg/kg) had no significant effect on heart rate (Fig. 2B), nor did it block nicotine-induced tachycardia when administered 30 min or 24 h prior (Fig. 4B). There was no significant effect of 10 mg/kg chlorisondamine to block the tachycardic effect of nicotine at 30 min however, there was a significant attenuation at 24 h ($p < 0.05$) (Fig. 4B) and 3 days ($p < 0.001$) (Fig. 4C). Chlorisondamine (10 mg/kg) alone raised heart rate (Fig. 2B) and enhanced the tachycardic effect of the lowest doses of nicotine (0.01 and 0.032 mg/kg), but did not affect the higher doses of nicotine (Fig. 4C).

Mecamylamine (1 and 10 mg/kg) administered alone lowered heart rate (Fig. 1D). Mecamylamine (1 mg/kg, 30 min) significantly blocked the increases in heart rate caused by nicotine ($p < 0.001$), but 10 mg/kg (24 h) did not (Fig. 4D).

Discussion

These experiments examined the ganglionic effects of high doses of chlorisondamine utilizing changes in heart rate and blood pressure as measures of ganglionic blockade. Blood pressure and heart rate were compared among several doses of chlorisondamine and mecamlamine to evaluate the degree of ganglionic blockade. The duration of chlorisondamine's ganglionic blockade was assessed by administering chlorisondamine or mecamlamine either 30 min, 24 h, or 3 days before nicotinic-induced stimulation of blood pressure and heart rate.

There are intense effects associated with 10 mg/kg, but not 1 mg/kg, chlorisondamine in the pigeon; these include increased breathing, loss of balance, and prostration (unpublished observation). These effects are not likely to be due to changes in blood pressure because 1 and 10 mg/kg chlorisondamine lowered blood pressure to a similar extent. Only the high dose of chlorisondamine (10 mg/kg) raised heart rate for 90 minutes, however, the increase in heart rate is unlikely to account for the physiological effects observed because it diminished before the onset of the other effects. Chlorisondamine is reported to cause decreases in blood pressure among several species regardless of route of administration: humans (100 mg, oral) (Grimson et al., 1955); monkeys (0.32 – 5 mg/kg, iv) (Tella et al., 1993); dogs (0.1 – 3 mg/kg, iv) (Maxwell et al., 1956); rabbits (0.32 mg/kg, iv) (Maxwell et al., 1958); and rats (2.5 – 5 mg/kg, iv or ia) (Abdel-Rahman, 1989, Kiritsy-Roy et al., 1990, Tella et al., 1992, Houdi et al., 1995, and Santajuliana et al., 1996). In the current study, the depressor effect of chlorisondamine reached its maximum at 1 mg/kg, but the peak change in heart rate occurred following 10 mg/kg chlorisondamine.

Control of heart rate is particularly complex, readily susceptible to both direct and reflex actions. This may explain the observation that the effects of chlorisondamine on heart rate were more variable than on blood pressure. Chlorisondamine produced dose dependent effects, lowering (0.1 mg/kg, having no effect (1 mg/kg), or raising (10 mg/kg) heart rate. In other species chlorisondamine has been found to both lower and raise heart rate. Chlorisondamine raised heart rate in dogs (0.32 – 2 mg/kg, iv) (Maxwell et al., 1956, 1958), but in rats and monkeys, 1 – 5 mg/kg chlorisondamine caused a decrease in heart rate with iv or intrarterial (i.a.) administration (Abdel-Rahman, 1989, Tella et al., 1992, 1993, and Santajuliana et al., 1996). Chlorisondamine (10 mg/kg) may cause a more complete and/or persistent ganglionic blockade than lower doses of chlorisondamine or mecamlamine, blocking all autonomic signals following a decrease in blood pressure. This would explain a large reflex increase in heart rate, which was not observed with only a partial or short-lived ganglionic blockade caused by the lower doses of chlorisondamine or mecamlamine.

In the pigeon, control of heart rate is likely to be partly centrally mediated because chlorisondamine only blocked nicotine-induced tachycardia after administration 3 days prior (Fig. 4C), a time point when chlorisondamine blocks nicotinic effects on behavior (Chadman and Woods, 2001), but has no effect on blood pressure (Fig. 3C). Chlorisondamine is not expected to have access to the central nicotinic receptors at early time points due to its charged nature. Chlorisondamine did not attenuate the nicotine-induced tachycardia at 30 min pretreatment, in contrast to mecamlamine. Therefore, in this study the changes in heart rate appear to be due to both reflex action after lowered blood pressure and control from the central nervous system. Mecamlamine has ready access to both central and peripheral nicotinic

receptors and causes only a decrease in heart rate regardless of dose, reflecting action at both central and peripheral nicotinic receptors.

The persistence of the central blockade by chlorisondamine is its most unusual feature. Therefore, another question for this study was to evaluate the length of the ganglionic blockade by chlorisondamine. Chlorisondamine (10 mg/kg) blocks nicotinic effects on behavior in the pigeon for up to 4 days (Chadman & Woods, 2001). This dose of chlorisondamine blocked the nicotine-induced increase in blood pressure at both 30 min and 24 h, which diminished by 3 days. The duration of the ganglionic blockade by 10 mg/kg chlorisondamine is longer-lasting than the blockade by mecamylamine in the pigeon, but not as long as the central blockade.

The acute observable effects of 10 mg/kg chlorisondamine are more profound than those produced by 1 mg/kg chlorisondamine (personal observation). The lower dose of chlorisondamine also produces a blockade of nicotine-induced physiological effects for up to 48 h and nicotine-induced decreases in rate of food-reinforced pecking for 24 h (Chadman and Woods, 2001). This is not as long lasting as 10 mg/kg chlorisondamine but may be better tolerated. The decrease in blood pressure by these two doses of chlorisondamine is similar, but only 10 mg/kg causes a significant increase in heart rate. The two doses of chlorisondamine blocked the pressor and tachycardic effects of nicotine to a similar extent, but the blockade by 1 mg/kg is much shorter. Thus, 1 mg/kg chlorisondamine produced central nicotinic blockade of long duration but with fewer cardiovascular effects than 10 mg/kg chlorisondamine.

The observable physiological effects associated with 10 mg/kg chlorisondamine in the pigeon are more prominent than those associated with 1 mg/kg. However, 10 mg/kg chlorisondamine does not appear to produce a larger degree of ganglionic blockade than 1 mg/kg, as measured by blood pressure. It may be that blood pressure cannot be lowered beyond

that of 1 mg/kg chlorisondamine so that any larger degree blockade by 10 mg/kg chlorisondamine was not able to be detected. Therefore, it will be useful to use other measures of ganglionic blockade, such as mydriasis or ptosis, to evaluate the large dose of chlorisondamine.

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Footnotes

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Figure. 1 The effect of saline, chlorisondamine and mecamlamine on blood pressure (A, C) and heart rate (B,D) in the pigeon. Drug injections were administered at time 0 and recorded for 2 h. Baseline blood pressure and heart rate values were subtracted from each individual pigeon and expressed as change from baseline over time (n = 8, each). Data were analyzed using one way ANOVA, Tukey's Multiple Comparison post test, $p < 0.05$ *; $p < 0.01$ **; and $p < 0.001$ ***.

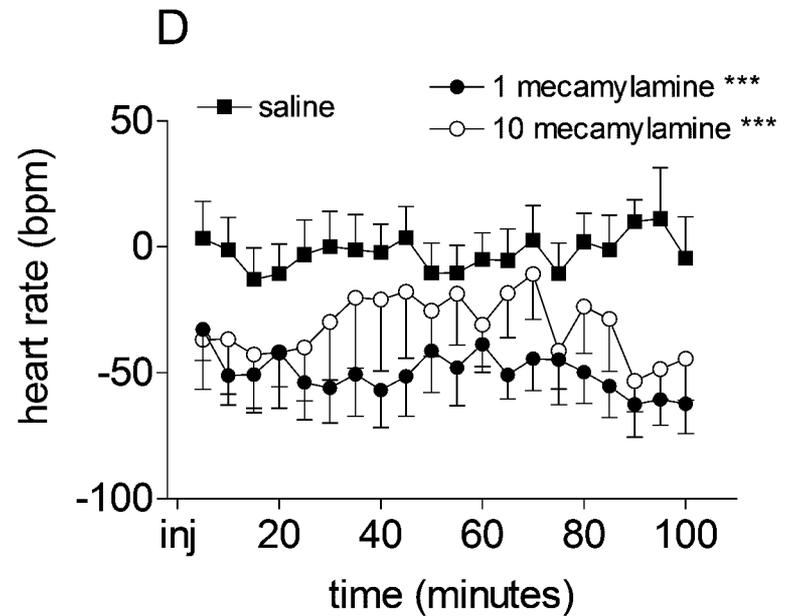
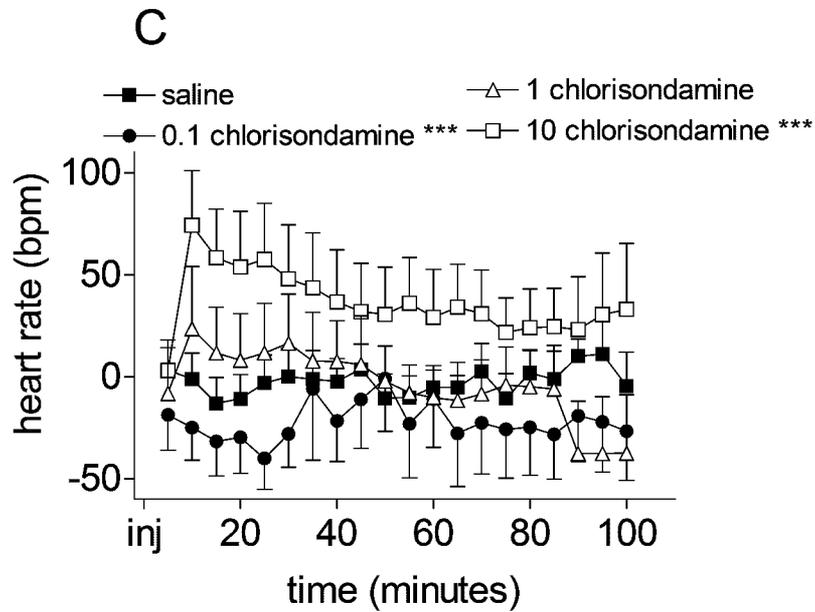
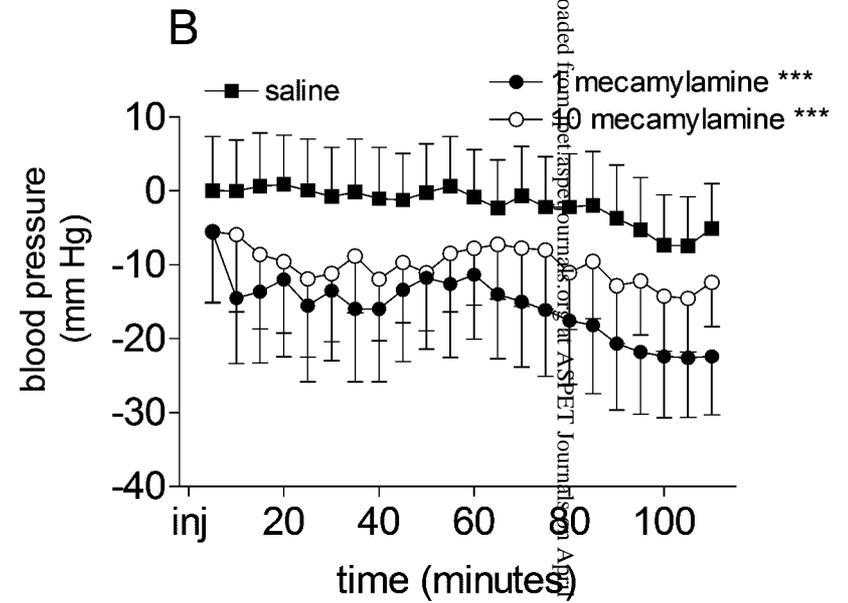
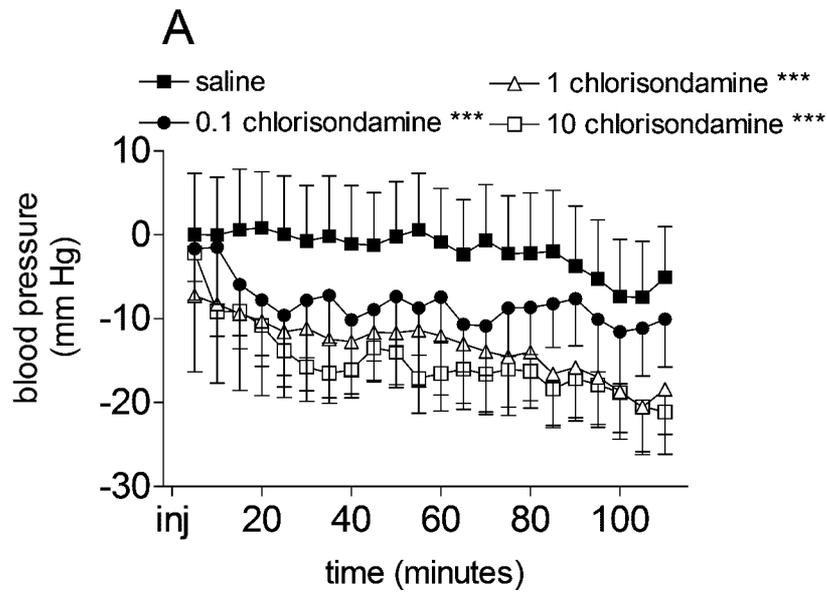
Figure. 2. Nicotine (n = 8-18) was administered in increasing doses and recorded for 20 min after each dose. As a control, saline (n = 7) was injected at the same time intervals as nicotine. The peak blood pressure and heart rate after each saline injection were calculated (insets) and used as the 100% baseline for Figs. 4 and 5.

Figure. 3 The effect of chlorisondamine and mecamlamine pretreatment on nicotine-induced increases in blood pressure. The peak blood pressure after each dose of nicotine was normalized to the saline baseline and compared among pretreatment groups. (A) 0.10 mg/kg chlorisondamine with 30 min and 24 h pretreatment. (B) 1 mg/kg chlorisondamine with 30 min and 24 h pretreatment. (C) 10 mg/kg chlorisondamine with 30 min, 24 h, and 3 day pretreatment. (D) 1 mg/kg mecamlamine with 30 min and 10 mg/kg mecamlamine with 24 h pretreatment. Data were analyzed using two-way ANOVA with Bonferroni's post-tests, $p < 0.05$ *; $p < 0.01$ **; and $p < 0.001$ ***.

Fig. 4 The effect of chlorisondamine and mecamlamine pretreatment on nicotine-induced increases in heart rate. The peak heart rate after each dose of nicotine was normalized to the

saline baseline and compared among pretreatment groups. (A) 0.10 mg/kg chlorisondamine with 30 min and 24 h pretreatment. (B) 1 mg/kg chlorisondamine with 30 min and 24 h pretreatment. (C) 10 mg/kg chlorisondamine with 30 min, 24 h, and 3 day pretreatment. (D) 1 mg/kg mecamlamine with 30 min and 10 mg/kg mecamlamine with 24 h pretreatment. Data were analyzed using two-way ANOVA with Bonferroni's post-tests, $p < 0.05$ *; $p < 0.01$ **; and $p < 0.001$ ***.

Figure 1



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Figure 2

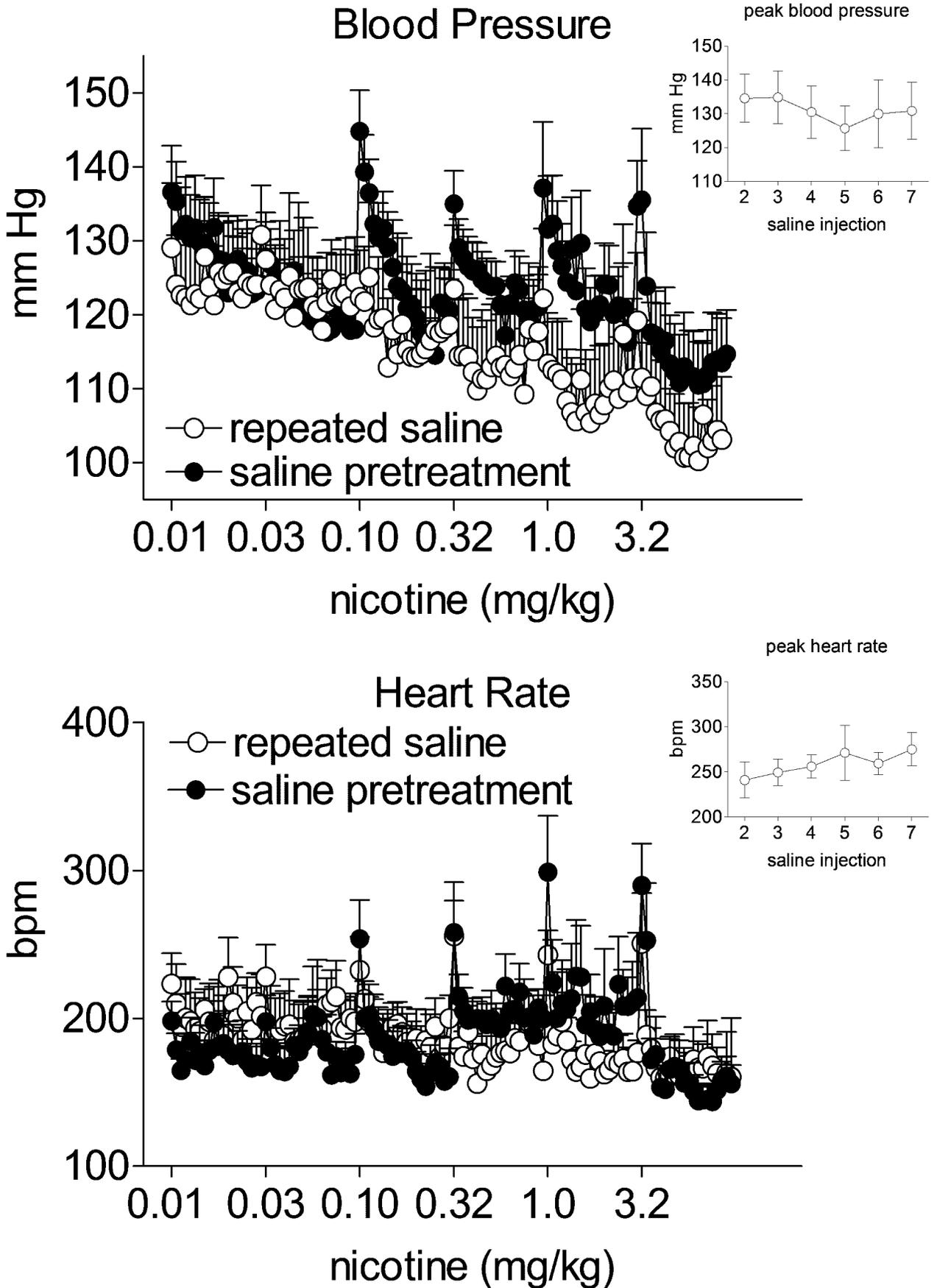


Figure 3

Peak Blood Pressure

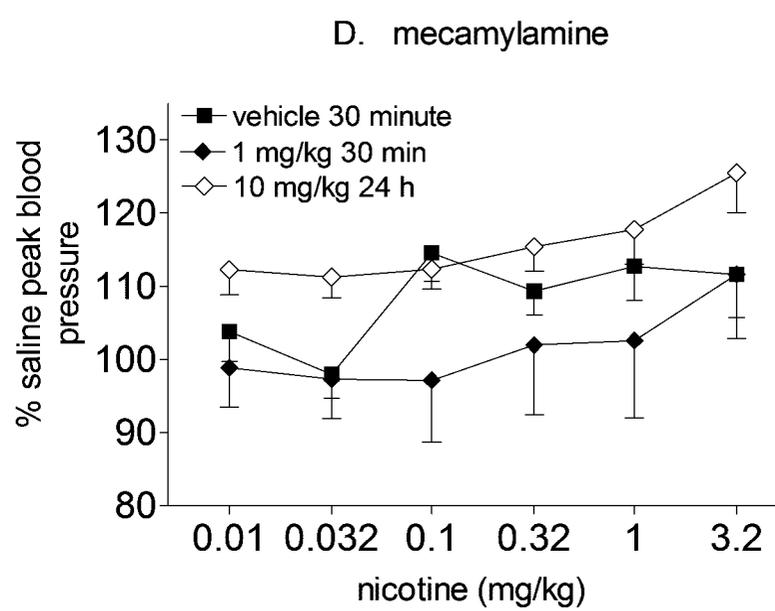
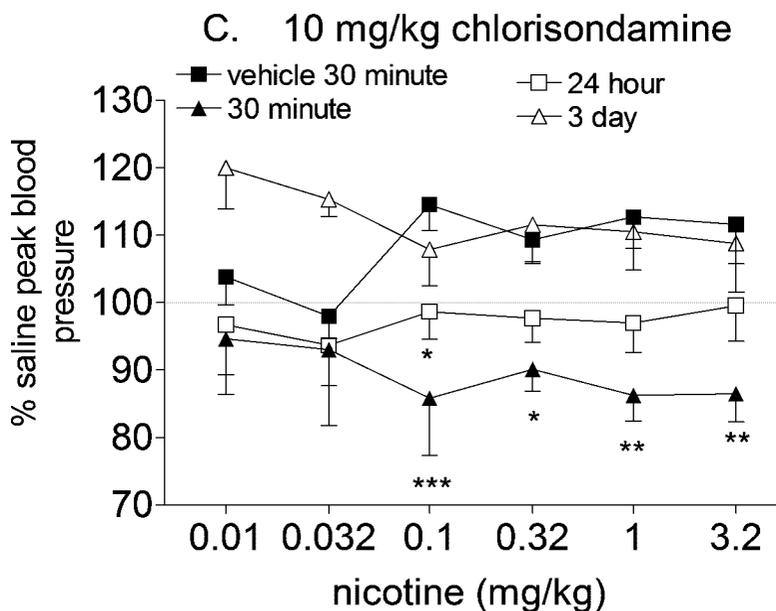
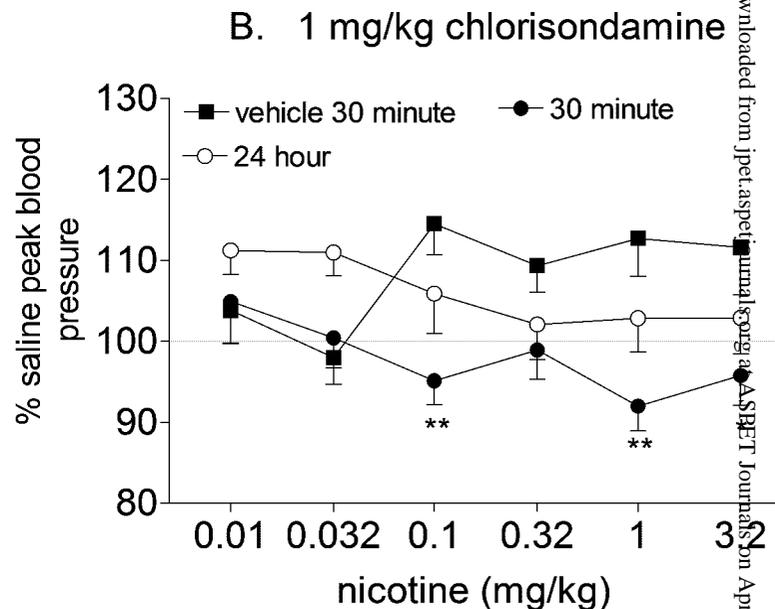
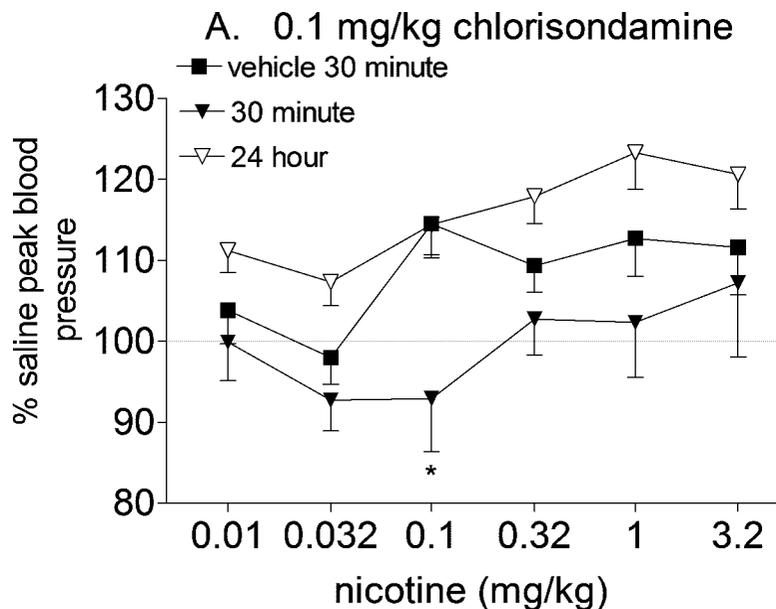
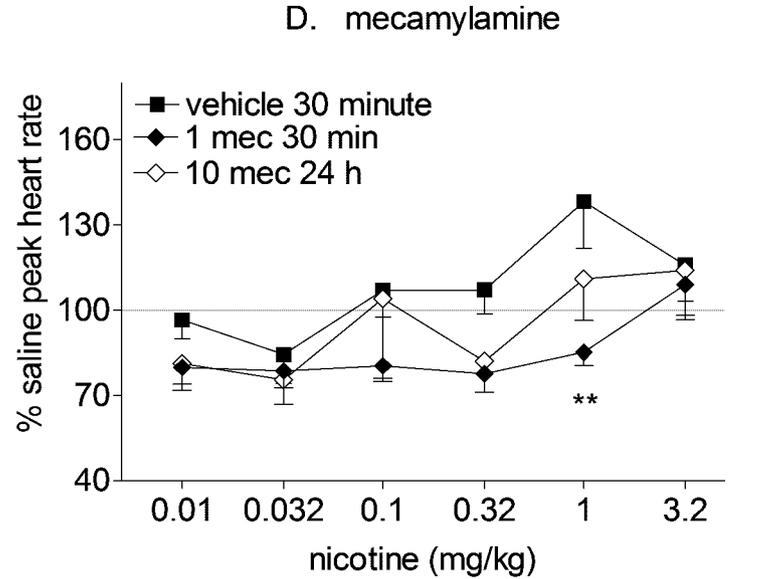
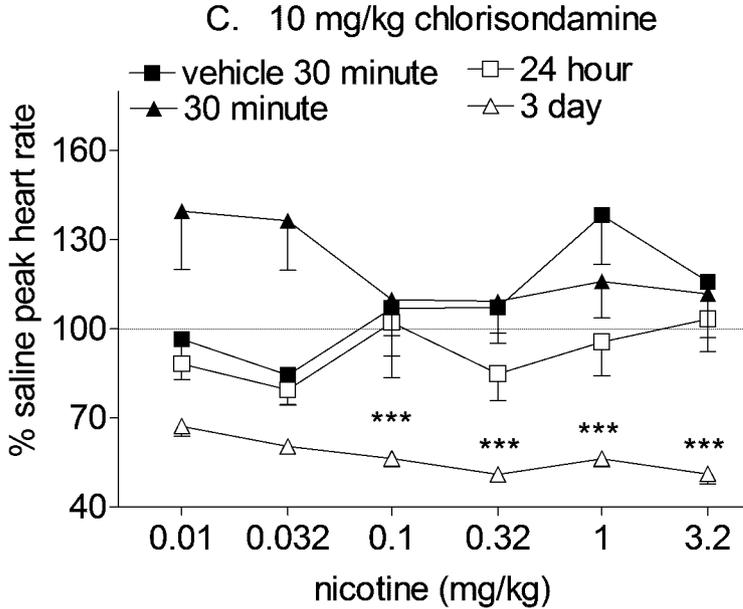
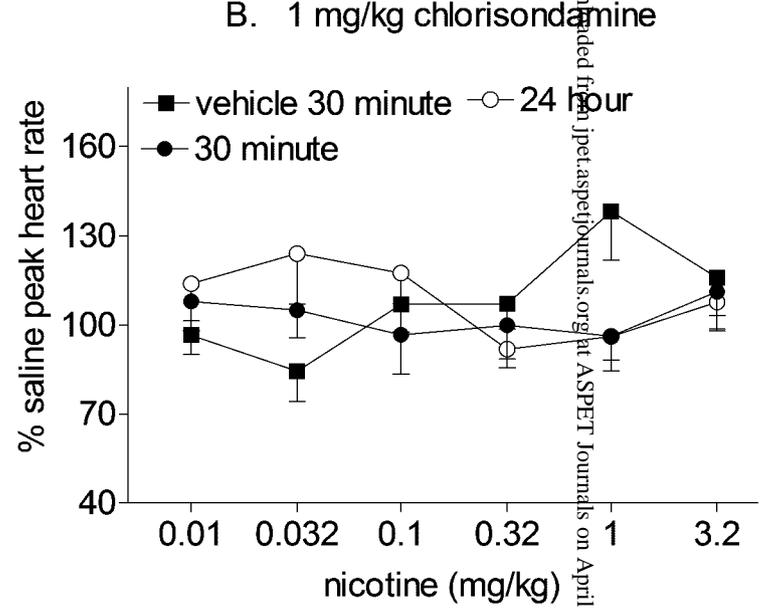
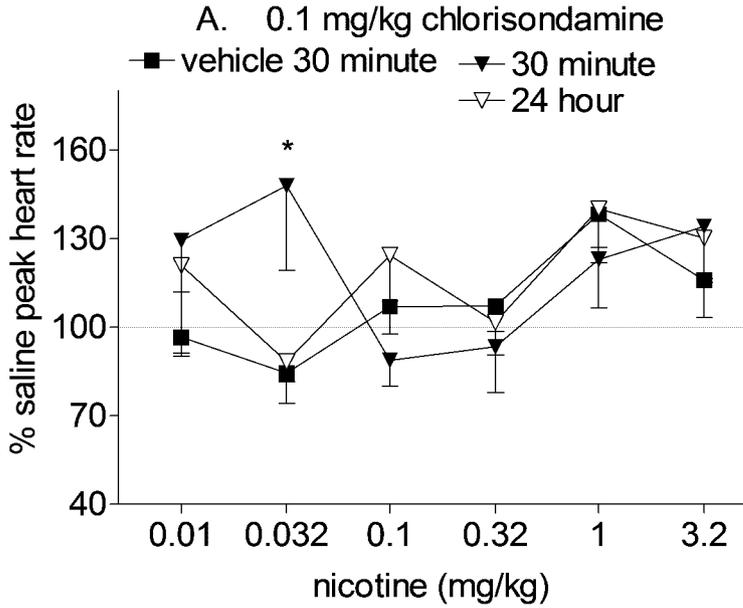


Figure 4

Peak Heart Rate



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