Sodium Lactate Elicits a Rapid Increase in Blood Pressure in Wistar Rats and Spontaneously Hypertensive Rats

Effect of Pretreatment with the Antipanic Drugs Clomipramine and Alprazolam

Ida Wikander, M.D., Tomas Roos, B.M., Anna Stakkestad, B.M., and Elias Eriksson, Ph.D.

Intravenous administration of sodium lactate in concentrations (0.5 M, 2 M) previously shown to elicit panic attacks in patients with panic disorder was found to cause a prompt and short-lasting increase in blood pressure in spontaneously hypertensive (SH) rats and in normotensive Wistar rats; in contrast, only weak and nonsignificant effects of lactate were observed in rats of the Sprague-Dawley strain. The effects of lactate on heart rate in SH rats varied; thus, whereas most rats displayed a modest bradycardia during lactate infusions, in some rats the increase in blood pressure was accompanied by an increase in heart rate. After pretreatment with

antipanic medication [the serotonin and noradrenaline reuptake inhibitor clomipramine (10 mg/kg/day, 3 weeks) or the triazolobenzodiazepine alprazolam (2 mg/kg/day, 3 weeks)], the blood pressure response to sodium lactate in SH rats was significantly blunted; in contrast, acute pretreatment with clomipramine (10 mg/kg) did not reduce the response. It is suggested that further studies on the cardiovascular effects of sodium lactate in SH or Wistar rats may shed further light on the mechanisms underlying the panic-provoking effect of lactate in panic disorder patients and on the mode of action of antipanic drugs. [Neuropsychopharmacology 12:245-250, 1995]

KEY WORDS: *Spontaneously hypertensive rat (SHR); Wistar rat; Sprague-Dawley rat; Sodium lactate; Blood pressure; Anxiety; Panic disorder; Clomipramine; Alprazolam*

In a majority of patients with panic disorder, administration of 0.5 M sodium lactate IV elicits an anxiety reaction strongly resembling the spontaneously occurring panic attacks. In contrast, the same concentration of sodium lactate does not induce anxiety attacks when administered to healthy controls (Liebowitz et al. 1984, 1985; Pitts and McClure 1967). Several studies have

shown that pretreatment with drugs that are effective in preventing spontaneous panic attacks also will protect the patient from lactate-induced panic (Carr et al. 1986; Cowley et al. 1991; Kelly et al. 1971; Rifkin et al. 1981; Yeragani et al. 1988).

Several hypotheses regarding the anxiogenic mechanism of action for sodium lactate have been put forward; for example, the effect has been attributed to changes in calcium concentrations (Pitts and McClure 1967), pH (Grosz and Farmer 1972), redox activity (Carr and Sheehan 1984), pCO₂ (Gorman et al. 1988), osmolarity (Jensen et al. 1991), and to the direct activation of a hyperresponsive suffocation alarm system (Klein 1993). Needless to say, the development of an animal model of lactate-induced panic would facilitate the evaluation of these and other theories; also, such an animal model may prove useful for investigating the mode of action of antipanic medication.

From the Department of Pharmacology, University of Göteborg, Göteborg, Sweden.

Address correspondence to: Elias Eriksson, Department of Pharmacology, University of Göteborg, Medicinaregatan 7, S-413 90 Göteborg, Sweden

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Whereas investigations on the possible anxiogenic effects of lactate in rodents are sparse, Friedman and collaborators (1988) have shown that sodium lactate elicits a paniclike behavior in nonhuman primates; moreover, this response was prevented by pretreatment with antipanic drugs (imipramine and alprazolam, respectively). In the search for a possible anxiety-related effect of lactate in rats, in the present study the effects of intravenously administered sodium lactate on blood pressure and heart rate in Sprague-Dawley rats, Wistar rats, and spontaneously hypertensive (SH) rats were investigated. In addition, the effects of pretreatment with either of the two antipanic drugs, alprazolam and clomipramine, on the cardiovascular responses to lactate were studied.

MATERIALS AND METHODS

Sprague-Dawley rats (250–300 g) were purchased from B&K (Sollentuna, Sweden) whereas Wistar rats (250–300 g) and SH rats (250–300 g) were purchased from Møllegaard, Ejby, Denmark. Before the experiments, the rats were kept under controlled conditions (temperature 21–22°C, humidity 55–65%, light on from 5 A.M. to 7 P.M.) with six animals in each cage. One IV (v. jugularis) and one intraarterial (a. carotis) cannula were implanted during chloral hydrate anesthesia one day before the administration of lactate. At the day of the acute experiment, blood pressure and heart rate were recorded by means of the arterial cannula and a pressure transducer connected to a Grass polygraph. After the recording of baseline blood pressure for at least 1 hour, and until baseline blood pressure had been stable for at least 30 minutes, an IV infusion of sodium lactate (0.5 or 2 M; 1 ml/5 minutes) or saline was started; 7 minutes later the infusion was stopped. The difference between baseline mean blood pressure and the level on which the mean blood pressure had stabilized during infusion was used as a measure of infusion induced changes in blood pressure. Heart rate was registered before and 5 minutes after the onset of infusion.

In the first experiment, the effects of two different concentrations of sodium lactate (0.5 M, 2 M) on blood pressure and heart rate in SH rats were studied.

In the second experiment, three different rat strains (SH rats, Wistar rats, and Sprague-Dawley rats) were compared with respect to the effect of 0.5 M sodium lactate on blood pressure.

In the third experiment, an osmotic minipump was implanted subcutaneously at the back of SH rats during anaesthesia with xylacine/ketamin. In one group of animals, the minipumps were loaded to cause an even release of clomipramine (Ciba, Västra Frölunda, Sweden) (10 mg/kg/day, dissolved in saline) for 4 weeks, whereas in the control group, the minipumps

were filled with vehicle only. Twenty-one to twenty-three days after the implantation of the minipumps, the rats were exposed to 0.5 M sodium lactate as described.

In the fourth experiment, Wistar rats were pretreated daily (IP) for 21 to 25 days with clomipramine (10 mg/kg/day) or alprazolam (Upjohn, Partille, Sweden) (2 mg/kg/day, dissolved in HCl + saline) or vehicle. The last injection was given approximately 1 hour before the administration of sodium lactate.

In the fifth experiment, the effects of a single dose of clomipramine (10 mg/kg IP, 60 minutes) or saline on the increase in blood pressure elicited by 0.5 M sodium lactate in SH rats were investigated.

Differences between groups were statistically evaluated using Student's *t* test (= 2 groups) or analyses of variance (ANOVAs) followed by Fisher's PLSD-test (> 2 groups). All group values are given as mean $\pm$ SEM.

RESULTS

Experiment 1

In SH rats administration of sodium lactate (0.5 M, 2 M; infusion rate: 1 ml/5 minutes, infusion time: 7 minutes) induced a prompt increase in blood pressure (Table 1), reaching a maximum usually within 3 minutes after the onset of infusion; when the infusion was stopped, blood pressure normally returned to baseline levels within a few minutes.

Administration of lactate usually induced a bradycardia of varying magnitude; however, in some rats, heart rate was unchanged or even increased (Table 1). Administration of 0.9% NaCl, with the same infusion rate, did not affect either blood pressure or heart rate (data not shown).

Experiment 2

Whereas IV administration of 0.5 M sodium lactate (infusion rate: 1 ml/5 minutes; infusion time: 7 minutes) caused a significant increase in blood pressure in SH and Wistar rats, in rats of the Sprague-Dawley strain, lactate induced a weak and nonsignificant pressor response only (Figure 1). Infusion of 0.9% NaCl induced no marked changes in blood pressure in any of the rat strains investigated. For statistics, see the legend to Figure 1.

Experiment 3

Administration of clomipramine to SH rats for 3 weeks by means of an osmotic minipump (10 mg/kg/day) did not affect baseline blood pressure (data not shown) but reduced the pressor response to lactate. Thus in rats pretreated with saline, the increase in blood pressure

Table 1. Mean Blood Pressure (mm Hg) and Heart Rate (bpm) before (Baseline) and during Infusion of Sodium Lactate (0.5 or 2 M) in Individual Spontaneously Hypertensive Rats

Baseline		0.5 M Lactate	
Blood Pressure	Heart Rate	Blood Pressure	Heart Rate
130	360	+15	-15
130	375	+25	±0
120	435	+23	-8
135	435	+12	-20
130	420	+10	+7
148	465	+10	-45
135	450	+10	-30
117	442	+23	-22
127	322	+41	+8
Mean ± SEM		+19.3 ± 3	-14 ± 6

		2 M Lactate	
		Blood Pressure	Heart Rate
140	435	+17	-19
120	450	+12	-30
133	382	+19	-37
117	397	+18	-7
143	375	+17	+30
115	330	+40	+30
150	420	+20	+37
155	420	+20	-8
130	420	+25	-8
115	420	+17	-23
126	450	+27	-23
160	345	+20	+30
Mean ± SEM		+21 ± 2	-2 ± 8

Figure 1. Effect of IV infusion of sodium lactate 0.5 M (L) or saline (S) on blood pressure in spontaneously hypertensive rats (SHR), Wistar rats (W), and Sprague-Dawley rats (SD). Bars represent mean (± SEM) change from baseline blood pressure. $n = 6-7$ in each group. p -Values indicate statistical significance of the difference in blood pressure increase between sodium lactate-treated animals and animals of the same strain given saline (ANOVA followed by Fisher's PLSD-Test; $F = 9.5$).

Figure 2. Effect of IV infusion of sodium lactate (0.5 M) on blood pressure in SH rats pretreated for ≥ 3 weeks with clomipramine (CLOM), alprazolam (ALP), or saline (Controls). Bars represent mean ($\pm$ SEM) increase from baseline blood pressure. $n = 5$ –10 in each group. p -Values indicate statistical significance of the difference versus controls (ANOVA followed by Fisher's PLSD-test; $F = 18.5$).

after administration of lactate was 18.2 ± 2.9 mm Hg whereas in rats pretreated with clomipramine the response was 7.3 ± 2.9 mm Hg ($n = 6$ –7, $t = 3$, $p < .02$; Student's t test).

Experiment 4

Repeated administration of clomipramine (10 mg/kg/day IP, 25–30 days) or alprazolam (2 mg/kg/day IP, 25–30 days) had no significant effect on baseline blood pressure (data not shown) but effectively antagonized the hypertensive response to lactate (Figure 2). For statistics, see the legend to Figure 2.

Experiment 5

Administration of a single dose of clomipramine (10 mg/kg, IP, 60 minutes) to SH rats influenced neither baseline blood pressure (data not shown) nor the increase in blood pressure elicited by lactate (0.5 M, IV) (Δ mm Hg: controls 18 ± 5 , $n = 5$; clomipramine 19 ± 7 , $n = 5$).

DISCUSSION

An increase in blood pressure that is due to a peripherally elicited vasoconstriction is usually accompanied by a baroreceptor-induced bradycardia (Folkow 1989; Spyer 1981). Albeit most rats administered 0.5 M sodium lactate indeed displayed a moderate decrease in heart rate, this response was not consistent; thus, in

some animals, no change in heart rate was observed in spite of a marked increase in blood pressure, while in others the pressor response was accompanied by tachycardia. In particular, rats given the higher concentration of lactate (2 M) not seldom responded with a marked increase in heart rate. This lack of a consistent compensatory bradycardia supports the involvement of the central nervous system in sodium lactate-induced hypertension.

In man spontaneous and lactate-induced panic are often, but not always, accompanied by an increase in blood pressure as well as in heart rate (Gaffney et al. 1988; Gorman et al. 1987, 1990; Yeragani et al. 1989); in contrast, most studies addressing the role of sympathetic activity in lactate-induced panic have failed to show a clear increase in plasma catecholamines after lactate administration (Liebowitz et al. 1985). Moreover, the heart rate response to lactate cannot be antagonized by a beta-receptor antagonist (Gorman et al. 1984). In a study by George and coworkers (1989), lactate infusions in panic disorder patients were shown to cause a marked decrease in vagal tone; however, such an effect could not be demonstrated by Gorman and coworkers (1987).

In rat as well as in man, the combined suppression of vagal activity and increase in sympathetic activity characterizing "defense reactions" leads to an increase in blood pressure as well as in heart rate; in contrast, the so-called freezing reaction and emotional depressor reaction ("playing dead") are characterized by pronounced bradycardia with no change and a decrease in blood pressure, respectively (Folkow 1993). The cardiovascular response to sodium lactate in the present study, being characterized by an increase in blood pressure with no consistent tachycardia, thus resembles neither the "defense reaction" nor the "freezing" or the "emotional depressor" reactions. Indeed, as pointed out by Klein (1993), the anxiety response elicited by lactate in man also is not equivalent to any classical fear response since dyspnea is always a central feature of spontaneous or lactate-induced panic anxiety, but not of fear reactions. Moreover, panic attacks, in contrast to fear reactions, are not accompanied by an activation of the hypothalamic-pituitary-adrenal axis (Klein 1993). In the present study lactate infusion, but not infusion of saline, had a wakening effect in sleeping rats; otherwise, no overt behavioral effects were observed.

Several authors have suggested that peripheral and/or central chemoreceptors are involved in the anxiogenic effects of lactate. Supporting this assumption, in panic disorder patients, as well as in controls, lactate uniformly induces an increase in respiratory rate (Klein 1993); moreover, in panic disorder patients, panic attacks can be elicited not only by sodium lactate but also by CO₂ exposure (Gorman et al. 1988). Via different reflexes, activation of carotid and aortic chemorecep-

tors may induce either bradycardia or tachycardia, depending, for example, on whether respiration is suppressed (as during diving) or allowed to increase (Blix and Folkow 1983). Moreover, stimulation of chemoreceptors may induce the cardiovascular and behavioral reactions usually observed after activation of defense alarm areas in the hypothalamus and amygdala (Bizzi et al. 1961; Hilton and Marshall 1982; see also Banks and Harris 1988). Given these complex influences of peripheral chemoreceptors on cardiovascular function, an involvement of chemoreceptors in the response to sodium lactate would be highly compatible with the variable changes in heart rate observed in the present study. Supporting this concept, as judged by gross observation of the animals, the increase in blood pressure observed in SH rats given sodium lactate was indeed accompanied by an increase in respiration rate. Interestingly, Franchini and Krieger (1993) recently reported that a potassium cyanide-induced activation of carotid body chemoreceptors in awake Wistar rats induced increased alertness, an increase in respiration rate, an increase in blood pressure and tachycardia or bradycardia (depending on dose); that is, a response pattern very similar to that observed after lactate infusion in the present experiments.

The pressor response to sodium lactate was observed in SH rats and Wistar rats, but not in rats of the Sprague-Dawley strain; thus, for further studies on the cardiovascular effects of sodium lactate, Sprague-Dawley is obviously not the strain of choice. Marked differences between various rat strains with respect to cardiovascular and behavioral reactivity have previously been reported by many researchers (Osadchuk et al. 1979; Pare 1989).

Alprazolam is a triazolobenzodiazepine displaying high affinity for benzodiazepine receptors and hence facilitating GABA-induced influx of chloride ions. Whereas the efficacy of conventional benzodiazepines in the treatment of panic disorder is still a matter of controversy, a large number of studies have shown that long-term treatment of alprazolam effectively prevents spontaneous (Rosenberg 1993) as well as lactate-induced (Carr et al. 1986; Cowley et al. 1991) panic anxiety. Antidepressant drugs also effectively prevent spontaneous (Eriksson and Humble 1990) as well as lactate-induced (Rifkin et al. 1981; Yeragani et al. 1988) panic attacks in patients with panic disorder. Among the tricyclic antidepressants, clomipramine appears particularly effective in this respect; thus, recent data indicate that clomipramine is, for example, considerably more potent and/or effective than imipramine in preventing panic attacks (Modigh et al. 1992). In all likelihood, the antipanic effects of clomipramine and other antidepressant drugs are due to a facilitation of serotonergic neurotransmission in brain (Eriksson and Humble 1990; Modigh et al. 1992). Thus, although both

alprazolam and clomipramine are effective in reducing panic attacks, they probably exert this clinical effect by entirely different primary modes of action.

The finding that both alprazolam and clomipramine administered for 3 weeks or longer effectively reduced the pressor response to sodium lactate suggests that similar mechanisms may be involved in the panicogenic effect of lactate in humans as in the pressor effects of lactate in SH and Wistar rats. Since the antipanic efficacy of clomipramine requires several weeks of medication, the observation that acute pretreatment with clomipramine did not influence the lactate-induced increase in blood pressure in SH rats lends some support for this concept. The possibility that alprazolam and clomipramine may influence the cardiovascular responses to lactate by mechanisms unrelated to their antipanic effects should, however, be emphasized; for example, clomipramine interacts not only with serotonin synapses in brain but also acts as an antagonist at cholinergic and α -adrenergic receptors.

In ongoing studies the effects of more specific pharmacological tools on the cardiovascular and respiratory effects of lactate in Wistar and SH rats are being examined; in addition, the central neurochemical events accompanying the sodium lactate-induced increase in blood pressure are being investigated.

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