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The Acute Effects of Amitriptyline, Iprindole and Trazodone on Blood Pressure and Heart Rate in Rats

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RICHARDSON, J. S. AND E. K. Y. CHIU. *The acute effects of amitriptyline, iprindole and trazodone on blood pressure and heart rate in rats.* PHARMAC. BIOCHEM. BEHAV. 17(6) 1221–1223, 1982.—The cardiovascular effects of the tricyclic anti-depressant amitriptyline, a monoamine uptake inhibitor, and iprindole and trazodone, two novel anti-depressants of unknown mechanism, were monitored in urethane anesthetized rats following intravenous (IV) or intracerebroventricular (IVT) injection. Amitriptyline (2 mg IV or 0.25 mg IVT) produced hypotension that might reflect an action of norepinephrine on the anterior hypothalamus. Iprindole (2 mg IV) produced hypertension and (0.25 mg IVT) tachycardia that is consistent with a partial beta-agonist mechanism. Trazodone (1 mg IV or 0.25 mg IVT) produced hypotension and bradycardia that is consistent with the activation of noradrenergic neurons in the anterior hypothalamus perhaps as a result of trazodone acting on presynaptic alpha$_2$ receptors or on presynaptic serotonin receptors to increase the release of norepinephrine. All three of these anti-depressants have the potential to precipitate cardiovascular complications, particularly in patients with pre-existing cardiovascular abnormalities.

Blood pressure Heart rate Amitriptyline Iprindole Trazodone

THE tremendous development in recent psychiatric research is reflected in the number of new psychoactive drugs introduced each year. From a basic science point of view, these pharmaceutical additions are most intriguing when new drugs are found to possess pharmacodynamic actions that are distinctly different from those of the older drugs but yet have clinical actions that are quite similar. Classical anti-depressant drugs seem to act either by preventing the breakdown of neurotransmitter by inhibiting the enzyme monoamine oxidase (e.g., tranylcypromine) or by preventing the removal of released molecules of the neurotransmitter from the synapse by inhibiting the uptake system (e.g., amitriptyline). Recently, evidence has been accumulating that indicates that some of the newer anti-depressant drugs do not act as monoamine oxidase inhibitors or as monoamine uptake inhibitors but yet are clinically effective in treating endogenous depression. Among these novel anti-depressants are agents such as iprindole, mianserin and trazodone. From the clinical point of view, the pharmaceutical advances are most interesting if the new drugs act more quickly or are safer than the old drugs. One of the major concerns with the use of the traditional anti-depressants such as amitriptyline has been the potentially lethal cardiovascular effects. Some of the newer anti-depressant drugs such as trazodone [4,5] have been reported to have little or no effect on the cardiovascular system. To compare the cardiovascular effects of two novel (iprindole and trazodone) and one traditional (amitriptyline) anti-depressants, we examined the heart rate, blood pressure and EKG effects of these drugs injected intravenously (IV) or into the lateral cerebral ventricle (IVT) in urethane anesthetized rats. Amitriptyline is a classical tricyclic anti-depressant that blocks the uptake of norepinephrine and serotonin, has considerable anti-cholinergic activity, and produces cardiac toxicity in the form of arrhythmias and other EKG irregularities. Iprindole and trazodone are novel anti-depressant drugs and do not appear to block any uptake mechanisms or to inhibit any enzymes.

METHOD

Male Sprague-Dawley rats, weighing 250 to 350 g, were purchased from Canadian Breeding Laboratories, Montreal, and kept under standard animal colony conditions for at least one week. Each rat was anesthetized with 1.5 g/kg urethane IP, and heart rate and EKG were monitored with subdermal electrodes in the right forepaw and left hindpaw. Blood pressure was measured via a carotid cannula and a Statham pressure transducer, and injections of the anti-depressant drugs were made IV via a jugular vein cannula or IVT via a 26 gauge stainless steel cannula placed stereotaxically in the left lateral cerebral ventricle. For the IV injections, each rat received 0.5 ml saline containing 2 mg amitriptyline, 2 mg iprindole or 1 mg trazodone injected over a five minute period. The rats in the IVT groups received 250 μg of each drug in 25 μl saline injected at a rate of 5 μl per minute. Control rats received comparable injections of saline. The data were evaluated statistically by Student's *t*-test.

RESULTS

Following the IV injections of amitriptyline and

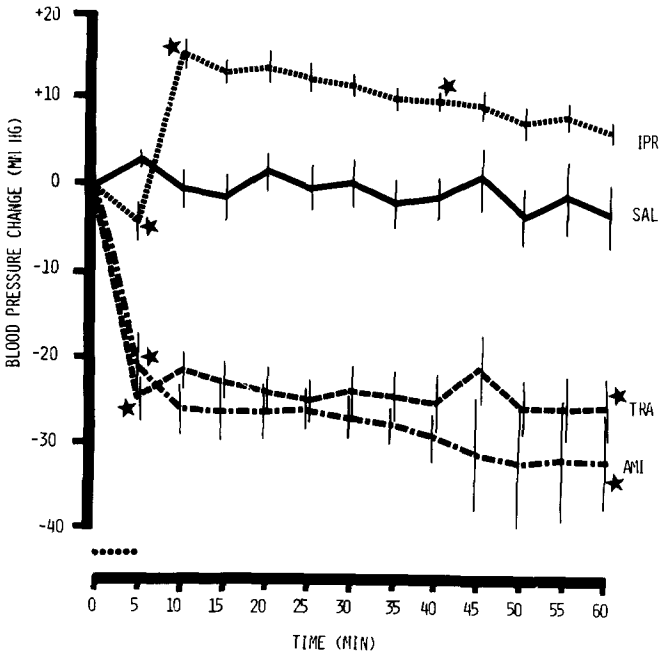

FIG. 1. Blood pressure of urethane anesthetized rats given intravenous injections of amitriptyline (AMI), iprindole (IPR), trazodone (TRA) or saline vehicle (SAL). Each data point represents the blood pressure change in 5 minute intervals from pre-injection baseline levels (mean±S.D.) of 5 to 7 rats. In this and all subsequent figures, points indicated with a star, and all data points between stars, are significantly different from the saline controls ($p<0.05$). The row of dots along the X axis marks the 5 minute period of drug infusion.

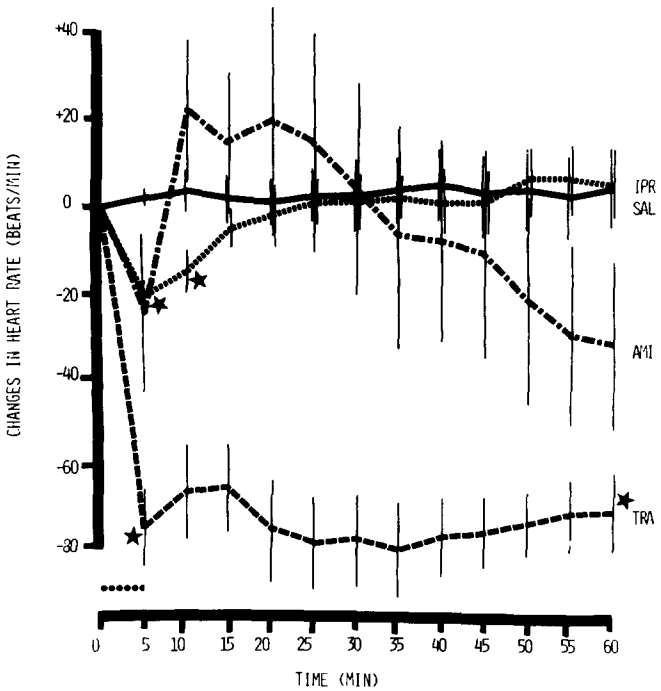

FIG. 2. Changes in heart rate from pre-injection baseline of the rats described in Figure 1.

trazodone, blood pressure (Fig. 1) quickly fell 20 to 30 mmHg below the saline controls where it stayed until the end of the experiment. However, IV iprindole had a distinctly different pattern. By the end of the infusion, blood pressure in the iprindole group had fallen 5 mmHg below control but then quickly rose to 15 mmHg above the controls and returned to control levels by the end of the experiment.

The heart rate effects of these drugs given IV are presented in Fig. 2. Trazodone has a marked bradycardic effect, lowering heart rate by about 80 beats per minute, that lasts at least one hour. Iprindole and amitriptyline produce a slight decrease in heart rate that lasts only about ten minutes. The only EKG abnormalities, a widening of the PR and the QRS intervals, were seen in the rats in the amitriptyline group.

When injected IVT (Fig. 3), trazodone and amitriptyline produce a hypotensive response within five minutes that is maintained until the end of the experiment. Blood pressure in the iprindole group remains at control levels for thirty minutes after the injection but falls significantly below controls over the last twenty-five minutes.

The heart rate effects of these drugs are quite variable (Fig. 4). Given IVT, amitriptyline has no effect on heart rate, while iprindole produces tachycardia and trazodone bradycardia. None of these drugs produced EKG irregularities following the IVT injection of 250 μg.

DISCUSSION

A comparison of the blood pressure and heart rate effects

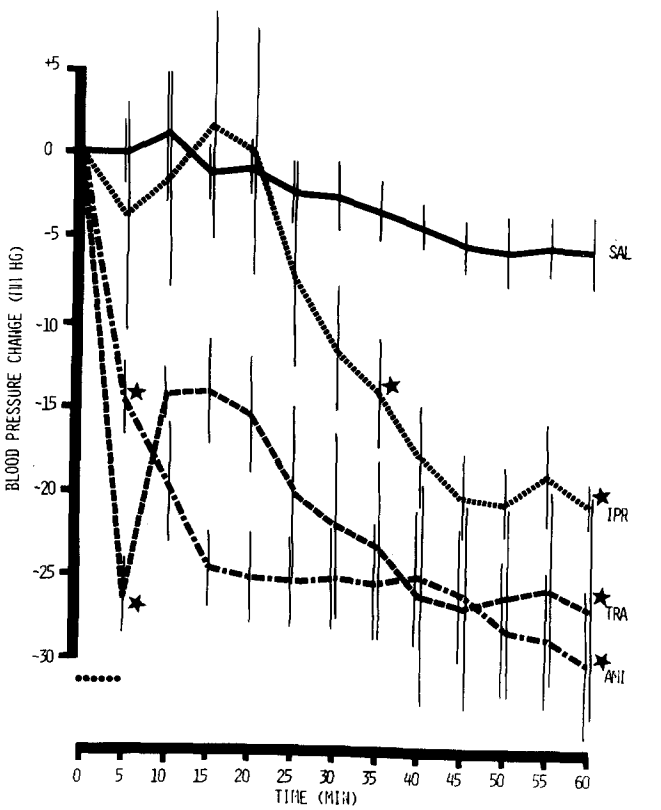

FIG. 3. Blood pressure change from pre-injection baseline in rats given injections of the drugs into the lateral cerebral ventricle. Data points represent the mean±S.D. of 5 to 7 rats in 5 minute intervals.

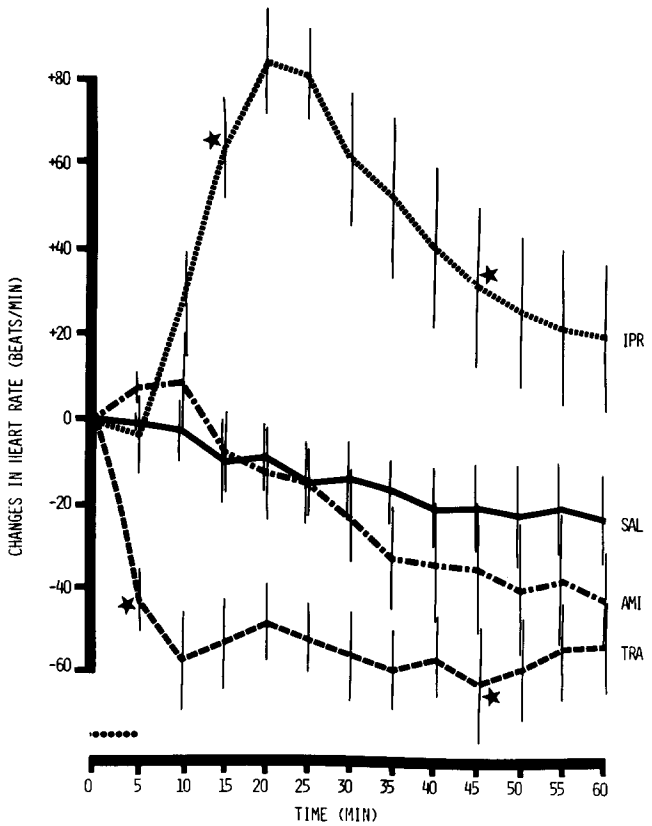

FIG. 4. Heart rate change in the rats described in Fig. 3.

of acutely administered amitriptyline, iprindole and trazodone in urethane anesthetized rats, demonstrates that each drug sufficiently disrupts the cardiovascular control mechanisms so as to have significant cardiovascular consequences. That each drug has a somewhat different effect on these cardiovascular parameters suggests that these drugs may be acting via different neurochemical mechanisms. Although the chronic administration of these drugs may have cardiovascular effects that are different from those reported here, the acute cardiovascular effects of iprindole and trazodone suggest that these novel anti-depressant drugs should be used clinically with the knowledge that these drugs can have serious cardiovascular complications [6], that may be especially hazardous in patients with underlying cardiac problems.

Since all three of these drugs are very lipophilic, the observed cardiovascular effects undoubtedly reflect components of both CNS and peripheral cardiovascular control mechanisms. However, any differences between injection routes would reflect factors more directly related to the relative predominance of drug effects on particular regional mechanisms. While pharmacology textbooks outline in great detail the peripheral mechanisms involved in cardiovascular regulation, the role of the brain in controlling heart rate and blood pressure is considerably less well understood. It has been known for some time that norepinephrine injected into the lateral or the third cerebral ventricles seems to act on alpha receptors in the anterior hypothalamus to produce a hypotensive and bradycardic response [1, 9, 10] that is mimicked by clonidine [3,9] or α-methyl-norepinephrine [10] and is blocked by phentolamine [2,9]. The IVT injection of the non-specific beta agonist isoproterenol [2] or the specific $beta_2$ agonist salbutamol [3] seems to activate beta receptors in the posterior hypothalamus to produce hypertension and tachycardia. Over the last few years, this picture has been further complicated by the demonstration of various types of receptors on the presynaptic nerve terminal that regulate the release of norepinephrine into the synapse [8]. These presynaptic receptors on adrenergic nerve terminals include autoreceptors of the $alpha_2$ type that inhibit the release of norepinephrine and of the beta type that facilitate release, as well as receptors for many other neurotransmitters such as serotonin, acetylcholine, enkephaline, etc. that have variable effects on the release of norepinephrine [7]. Consequently, the end result of any experimental manipulation of the adrenergic system will be determined by the interplay of mechanisms reflecting central versus peripheral, presynaptic versus postsynaptic, alpha versus beta, anterior hypothalamus versus posterior hypothalamus, drug effect versus homeostatic compensation, etc., influences.

The exact contribution of these factors and the interactions of the various components involved in cardiovascular control must be determined in future experiments.

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