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Cardiovascular Effect of Oxytocin in Rodents and a Marsupial.* (29013)

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Since synthetic oxytocin became available in 1953(1), a few studies have been made on the cardiovascular effects of the drug. It was found that oxytocin decreases arterial blood pressure, and increases cardiac output and regional blood flow in human subjects(2), dogs(3) and chickens(4). On the other hand, oxytocin was reported to increase arterial pressure in estrous and pregnant rats, while producing no change of blood pressure in male and non-estrous femal rats(5). It was also found that reserpine causes oxytocin to increase arterial pressure even in male and non-estrous female rats(5). The present study was undertaken to investigate the effect of increasing doses of oxytocin on arterial pressure in male rats with and without reserpine pretreatment, pregnant rats, guinea pigs and opossums, and the effects of oxytocin on both arterial pressure and regional vascular resistance in rabbits.

Methods. Male and pregnant rats of Holtzman strain weighing between 350 and 400 g, guinea pigs weighing about 500 g, rabbits weighing about 2 kg, and opossums weighing between 3.5 and 6.0 kg were anesthetized with i.p. or i.v. administration of sodium pentobarbital (30 mg/kg). Mean arterial pressure was continuously measured with a Statham pressure transducer (P25AA) from a cannulated femoral artery in rats, rabbits and opossums, and from a cannulated carotid artery in guinea pigs. In 10 male rats, reserpine (2.5 mg/kg) was given intraperitoneally daily for 2 days prior to the experiments. Wide ranges (0.05-3.2 U/kg) of synthetic oxytocin (Syntocinon) were administered to the animals, and its effect on mean arterial pressure was observed. In 6 rabbits, the effects of oxytocin on the regional circulation was studied. After laparotomy, the abdominal aorta was cannulated proximally and distally to form a loop. A Sigma-motor pump was interpolated in the middle of the loop, and the distal abdominal aorta was perfused at a known and constant rate. Before and following the i.a. injection of a single dose (0.1 U/kg) of oxytocin, mean systemic arte-

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rial pressure and perfusion pressure were measured continuously with Statham pressure transducers (P25AA). Arterial pressures were recorded continuously with either a Grass polygraph (model 5) or an Electronics for Medicine recorder (DR8).

Results. The average effects of graded doses (0.05-3.2 U/kg) of oxytocin in 4 species of animals are summarized in Fig. 1. Oxytocin increased mean arterial pressure in both male and female of each of the 4 species. The magnitude of increase was essentially in proportion to dose given. There was no significant difference between male and pregnant rats in the pressor response to oxytocin(Fig. 1). At any given dose of oxytocin, the increment in arterial pressure was greater in opossums than in 3 rodents studied. In all animals studied, there was no evidence of tachyphylaxis to the drug in regard to arterial pressure response. When male rats were pretreated with reserpine, mean arterial pressure decreased from a control value of 121 ± 4 (S.E.) mm Hg to 70 ± 2 mm Hg (Fig. 2). In these reserpinized rats, oxytocin always increased arterial pressure more markedly than it did in control rats. However, the maximum pressure attained in response to equivalent doses of oxytocin was always lower in reserpinized rats than in control rats.

Using a Sigmamotor pump, the effect of the i.a. injection of oxytocin (0.1 U/kg) on peripheral vascular resistance was studied in 6 rabbits. Oxytocin increased perfusion pressure in the vascular areas distal to the cannulated lower abdominal aorta, while systemic arterial pressure remained unchanged (Fig. 3). Thus, oxytocin increased peripheral vascular resistance, indicating clearly its vasoconstricting action.

Discussion. From this study it is evident that synthetic oxytocin always increases mean arterial pressure in both male and pregnant rats, guinea pigs, rabbits and also in opossums. These observations made on rats are not in accord with those of Lloyd and Pickford(4,5) who observed that oxytocin did not change arterial pressure in male and nonestrous female rats, although it increased pressure in estrous and pregnant rats. From

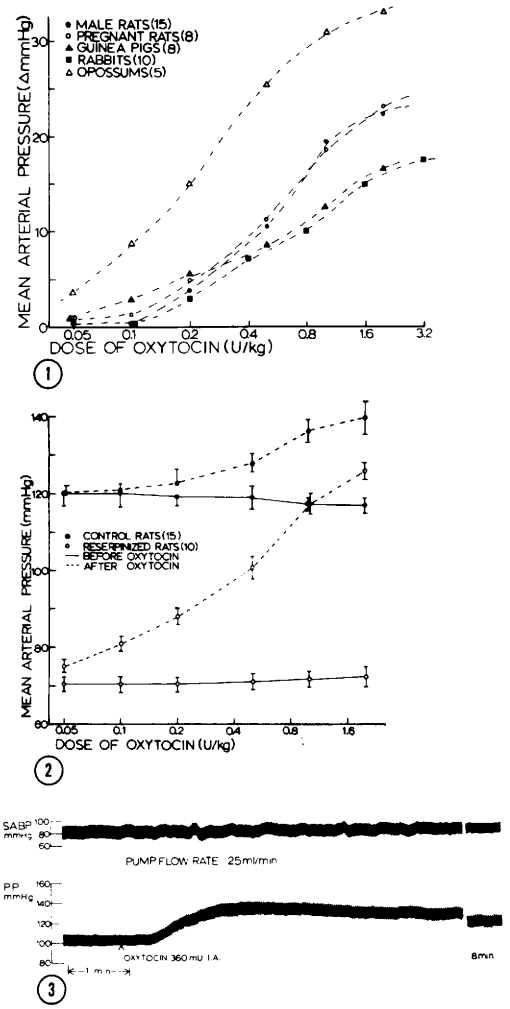

FIG. 1. Effect of the i.v. administration of oxytocin in geometrically increasing doses on mean arterial pressure in 15 male rats, 8 pregnant rats, 8 guinea pigs, 10 rabbits and 5 opossums. Each value in the graph represents the average of the maximal increases in mean arterial pressure after i.v. injection of oxytocin in each animal.

FIG. 2. Comparison of effect of i.v. administration of oxytocin in geometrically increasing doses on mean arterial pressure in 15 control male rats and 10 reserpinized male rats. Each dot or circle represents mean value of mean arterial pressure before and after i.v. injection of oxytocin. Standard errors of means are indicated by I-shaped lines(6).

FIG. 3. Effect of i.a. injection (abdominal aorta) of 360 mU/kg of oxytocin on regional circulation in a male rabbit. The abdominal aorta was perfused constantly at a rate of 25 ml/min with a Sigma motor pump. SABP denotes systemic arterial blood pressure. PP denotes perfusion pressure of the abdominal aorta peripheral to site of pump.

the measurement of arterial pressure alone Lloyd and Pickford postulated that oxytocin exerts a vasodilating action in male and non-estrous rats. The latter conclusion is not warranted on the basis of the data provided by Lloyd and Pickford, since they failed to measure cardiac output or regional blood flow together with arterial pressure. Obviously, it is impossible to determine the effect of a drug on peripheral vascular resistance without simultaneous measurements of the 2 hemodynamic parameters. Thus, it cannot be ascertained whether the drug is a vasodilator or constrictor. In the present study on rabbits, it was possible to perfuse the vascular beds at a constant flow rate via the cannulated lower abdominal aorta. Since the i.a. injection of oxytocin increased perfusion pressure significantly, it is evident that oxytocin did increase the peripheral vascular resistance by constricting the vascular trees in the perfused areas.

Lloyd and Pickford(5) found that oxytocin increased arterial pressure in reserpinized non-estrous rats. Hence, they concluded that reserpine causes oxytocin to become a vasoconstrictor in normal non-estrous rats. Reserpine in the doses employed lowered arterial pressure markedly in male rats presumably through its sympathetic blocking action. Subsequent injections of oxytocin increased arterial pressure more markedly than in control rats. However, the maximum arterial pressure attained following injection of oxytocin in reserpinized rats was always much lower than in control rats. It can be said, therefore, that the observation made on reserpinized rats may not be due to the reversal of action of oxytocin on the vascular smooth muscle in male or non-estrous rats, but rather to the greater responses of the vessels in these rats to oxytocin, simply because the vascular smooth muscles were more relaxed by reserpine.

The basic mechanisms, through which oxytocin dilates blood vessels in man, dogs and chickens, and constricts vessels in rodents, still remain uncertain. It was found that oxytocin produces either no change or a decrease in myocardial contractility in isolated guinea pig atria(3), and causes a greater increase in arterial pressure in reserpinized rats than in controls. Therefore, at least 2 possible factors, *i.e.*, the increased cardiac output by positive inotropic action and the catecholamine release by oxytocin, can be excluded as the causative mechanisms responsible for the hypertensive effect of oxytocin in rodents. In this laboratory, further study is under way to elucidate the precise pharmacodynamic mechanisms of the action of oxytocin on the peripheral vasculatures in different species under various pathophysiological conditions.

Summary. The effects of oxytocin on arterial pressure and regional circulation were studied in rats, guinea pigs, rabbits and opossums. It was found that oxytocin increased arterial pressure in all species of animals studied. The magnitude of the increase in pressure was essentially in proportion to the doses given, but was greater in opossums than in 3 rodents studied. Oxytocin always increased arterial pressure more markedly in reserpinized rats than in control rats. However, the maximal pressure attained following equivalent doses of oxytocin was always lower in reserpinized rats than in control rats. The i.a. injection of oxytocin was found to increase the peripheral vascular resistance in rabbits, indicating the vasoconstricting effect of the drug.

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