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0014-4754/87/080879-02$1.50 + 0.20/0

Lack of pressor effect of dopamine in the pentobarbital-anesthetized rat

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Summary. The blood pressure and heart rate responses to intravenous dopamine infusion at 2.5, 5.0 and 10.0 $\mu g \cdot min^{-1} \cdot 100\,g^{-1}$ were studied in conscious and pentobarbital-anesthetized Sprague – Dawley rats. In the conscious rats, dopamine caused a significant dose-related increase in the mean arterial blood pressure which was abolished in the anesthetized rats. The heart rate increased significantly only at the highest dose infused. The responses to equipressor doses of noradrenaline (40 $ng \cdot min^{-1} \cdot 100\,g^{-1}$) and phenylephrine (1.0 $\mu g \cdot min^{-1} \cdot 100\,g^{-1}$) were also suppressed in the anesthetized rats. The results suggest that pentobarbital anesthesia depresses the blood pressure response to dopamine infusion in the rat through a depression of activation of alpha-adrenoceptors.
Key words. Dopamine; blood pressure; heart rate; anesthesia.

Previous reports on the blood pressure effect of dopamine in the rat are scanty. A dose-related pressor effect has been described in the conscious rat[1]. This pressor effect of dopamine is, however, affected by various factors. Thus, on a low sodium diet, the blood pressure response in the conscious rat is attenuated[2]. Also, there is general agreement that the administration of dopamine causes a reduction of the blood pressure in animals pre-treated with alpha-adrenoceptor blocking angents[3,4]. This hypotensive response is thought to be due to vasodilation of the renal, mesenteric and coeliac beds[5], and/or partly due to the release of a dilator prostaglandin.[6]

In recent years, increased attention has been given to the importance of alteration in cardiovascular dynamics produced by general anesthesia[7,8]. In general, the cardiovascular system of the animal is depressed and the response to exogenous agents can be markedly affected by anesthesia[6]. The effect of anesthesia on the cardiovascular response to dopamine administration is unknown.

The purpose of this study, therefore, was to compare the blood pressure and heart rate responses to i.v. dopamine in the conscious and in the pentobarbital-anesthetized rat. To determine the role of alpha adrenoceptor stimulation in the response, equipressor doses of noradrenaline and phenylephrine were also used in the study.

Materials and methods. Eighty-two male Sprague-Dawley rats weighing between 120 and 240 g were used. The animals were bred and housed in the department under natural light and environmental conditions. They were allowed free access to a commercial feed (Pfizer Products, Lagos, Nigeria) and tap water to drink. They were subsequently divided into:

a) *Conscious rats:* Under sodium pentobarbital anesthesia (60 mg/kg, i.p.) two polyethylene catheters were inserted and secured: one into the right carotid artery, and the other into the left jugular vein. The free ends of the catheters were passed s.c. behind the ear on the right side of the neck and exteriorized. Catheters were filled with about 0.10 ml of heparinized saline (1000 units/ml), and plugged. The cut skin was sutured and the animal allowed to recover. 24 h later, when the animal was fully awake, the heparinized saline was removed from the catheters and discarded. A fresh 0.20 ml of heparinized saline was then injected to keep the carotid catheter patent, while through the jugular vein, 5% dextrose solution (154 mmol/l) was infused (Ealing Universal Infusion Pump, Walford, England) at a constant rate of 1.0 ml/h for 60 min (equilibration period); the last 20 min was taken as the pre-drug infusion period (Pre-drug). Thereafter, dopamine (3,4-dihydroxyphenylethylamine hydrochloride; Sigma Chemical Co., St. Louis, MO, USA) was infused at 2.5, 5.0 and 10 $\mu g \cdot min^{-1} \cdot 100\ g^{-1}$ for another 20 min (Experimental period). Dopamine was dissolved in 5% dextrose and infused at a constant rate of 1.0 ml/h. In the subsequent 20 min (Recovery period), 5% dextrose was again infused. In a control group of rats, 5% dextrose only was infused continuously for 60 min after the equilibration period. The pulsatile arterial blood pressure was measured via the carotid artery using Statham P23ID pressure transducer and recorded on a Gilson Model 5/6H-Polygraph at 0.1 mm/s chart speed. The mean arterial blood pressure was taken as the diastolic blood pressure plus one-third of the pulse pressure. To obtain the heart rate, the chart was speeded to 5.0 mm/s and the pulse peaks counted. During the infusion, all rats were unrestrained and put on a stainless steel pan to which they were accustomed prior to the experiment.

b) *Anesthetized rats:* Anesthesia was induced with sodium pentobarbital (60 mg/kg i.p.). The rats were placed on a thermostatically heated table that maintained the body temperature constant at 37.0 ± 0.5 °C. They were thereafter prepared for dopamine infusion as in the conscious group, except that in addition, the trachea was also intubated. After surgery, the animals were allowed at least 45 min of equilibration during which 5% dextrose was infused at 1.0 ml/h and the blood pressure had stabilized. At the end of the equilibration period, the pre-drug infusion data were recorded. The subsequent protocol was similar to that in the conscious rats. In another group of control rats, 5% dextrose was infused continuously for 60 min after the equilibration period.

c) Equipressor ($\simeq$ 40 mmHg increase in mean arterial blood pressure in the conscious rat) doses of noradrenaline (40 $ng \cdot min^{-1} \cdot 100\ g^{-1}$) and phenylephrine (1.0 $\mu g \cdot min^{-1} \cdot 100\ g^{-1}$) were also similarly infused in further groups of conscious and anesthetized rats. The conscious and anesthetized rats for noradrenaline and phenylephrine infusions were prepared as above.

Statistical analysis: All values are given as the mean ± SEM. The data were analyzed using Student's t-test with Dunnett's correction to the t-value. A p value less than 0.05 was considered significant.

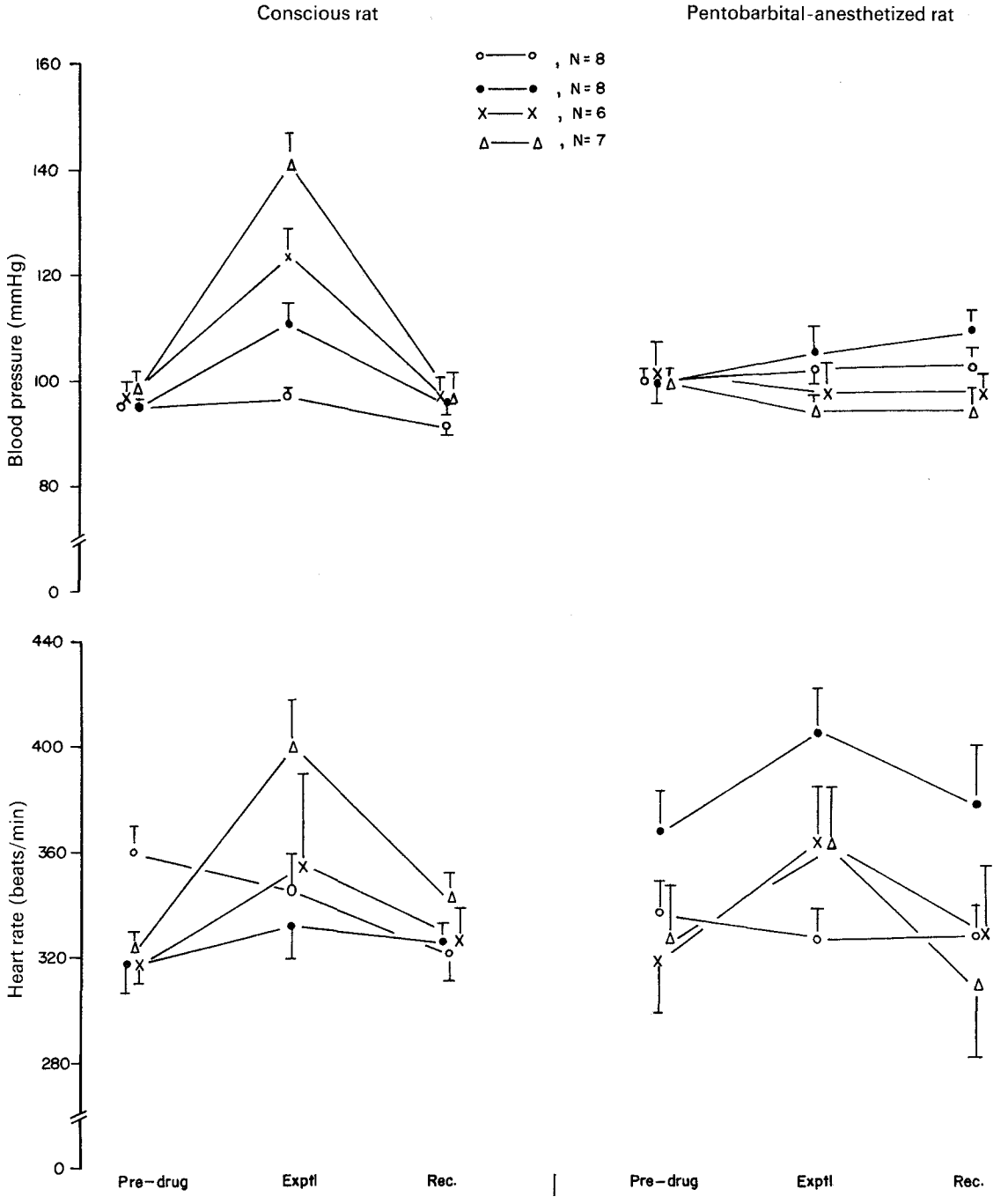

Figure 1. The effect of 5% dextrose (○——○) or dopamine (●——●, 2.5; ×——×, 5.0; and △——△, 10.0 $\mu g \cdot min^{-1} \cdot 100\ g^{-1}$) infusion on the blood pressure and heart rate of conscious and pentobartital-anesthetized rats. Values are means ± SEM. N = number of rats. Pre-drug, and Rec. represent the periods during which 5% dextrose was infused while Exptl represents the period during which dopamine or 5% dextrose was infused.

Results. Control rats. The infusion of 5% dextrose for 60 min did not significantly affect the blood pressure and heart rate in either the conscious or the anesthetized rats (fig. 1). The pre-infusion blood pressures and heart rates in the two groups of rats were also similar. Thus, anesthesia did not affect the basal blood pressure and heart rate of these rats.

Conscious rats. The infusion of dopamine caused a significant dose-related increased in the blood pressure (fig. 1). The peak rise in the pressure occurred between 3 and 5 min after starting the infusion. This peak pressure was maintained till the termination of the infusion. The blood pressures at the pre-drug infusion and recovery periods were not different. The heart rate increased only at the highest dose infused. Noradrenaline and phenylephrine also induced a significant increase in blood pressure but a significant fall in the heart rate (fig. 2).

Anesthetized rats. When dopamine was infused in the anesthetized rat, the blood pressure and heart rate were not significantly affected (fig. 1). Thus, pentobarbital anesthesia abolished the pressor effect of dopamine in the rat (fig. 2). Noradrenaline and phenylephrine still induced significant increases in the blood

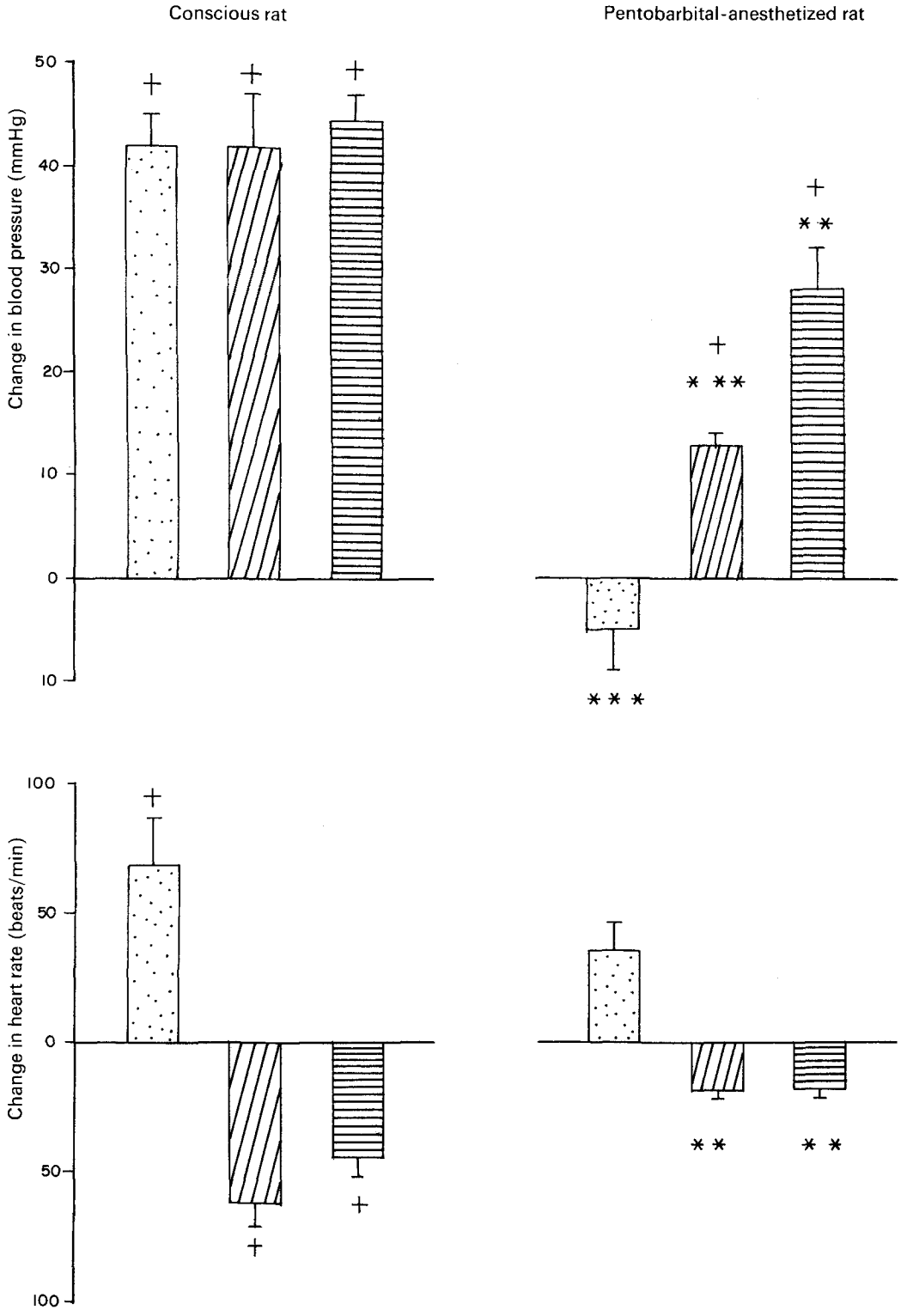

Figure 2. Change in blood pressure and heart rate with the infusion of equipressor doses of dopamine (▨, 10 μg. $min^{-1} \cdot 100\ g^{-1}$, N = 7) Noradrenaline (▨, 40 ng·$min^{-1} \cdot 100\ g^{-1}$, N = 6), and phenylephrine (▨, 1.0 μg·$min^{-1} \cdot 100\ g^{-1}$, N = 6) in conscious and pentobartital-anesthetized rats. Values are means ± SEM; N = number of rats. ** $p < 0.01$, *** $p < 0.001$, significantly different from the value in the conscious rat. +, significant increase or decrease from pre-drug values (see text).

pressure in the anesthetized rats; but the heart rate was not significantly affected. Figure 2 compares the equipressor responses in conscious and anesthetized rats. Anesthetization abolished or suppressed the blood pressure response to the equipressor doses of dopamine, noradrenaline and phenyleprhine. The decrease in heart rate was also significantly suppressed when noradrenaline and phenylephrine were infused in the anesthetized rats.

Discussion. Dopamine is the natural precursor of noradrenaline and it is a potent beta-adrenoceptor agonist. At relatively high doses, it also has alpha-adrenoceptor agonist activity[9]. However, it is unique to dopamine that it is able to selectively reduce renal and mesenteric vascular resistances[4,9]. This 'dopaminergic' effect cannot be blocked by propranolol or phenoxybenzamine[10,11]. Since dopamine exerts both pressor and depressor effects[9], the final effect will depend on the interaction of various factors. One of these factors is the level of sodium in the diet[2], and the present report shows the effect of yet another factor, anesthesia. The results show that in sodium pentobarbital anesthetized rats, the pressor response to i.v. dopamine is abolished. It is known that anesthesia, particularly with barbiturates, affects the regulation of blood pressure[12] as well as the animal's response to exogenous agents[6,7]. In addition, the blood pressure response to dopamine is also species-dependent. Thus, in anesthetized dogs, a large dose of dopamine results in a pressor response,[13] while a purely depressor response is observed in anesthetized rabbits and guinea pigs[4,14].

In constrast to the present study, Grabowska[15] showed that dopamine caused an increase in the blood pressure in the anesthetized Wistar rat. This contradiction may be due to the experimental set up. Grabowska[15] used urethane-anesthetized and bilaterally vagotomized Wistar rats. Furthermore, some test doses of dopamine were given i.p. In the study reported here, the pentobarbital-anesthetized Sprague-Dawley rats were not vagotomized, and all solutions were given i.v. It is unlikely that the type of anesthetic used could have contributed to the difference in response, since it has been shown that inactin and pentobarbital are equipotent in depressing the cardiovascular response to acute hemorrhage in the rat[16].

Except at the highest dose infused, and in the conscious state, dopamine did not significantly affect the heart rate, a result that is similar to the observation in the dog[13,17]. In man, large doses of dopamine cause an increase in arterial blood pressure and induce a reflex bradycardia[4,9].

The pressor action of dopamine has been linked to a direct activation of the alpha-adrenoceptors[1,18]. Since this pressor effect of dopamine is abolished in anesthetized rats, it is reasonable to assume that anesthesia suppresses the activation of the alpha-adrenoceptors. This is supported by the observation in this study that equipressor responses to noradrenaline and phenylephrine are also suppressed in the anesthetized rat. Noradrenaline and phenylephrine are known to increase the blood pressure specifically by a generalized vasconstriction via the activation of alpha-adrenoceptors, with a consequent reflex bradycardia. It is interesting to note that even this reflex bradycardia is also suppressed by anesthetization. Since anesthetization suppressed the increase in blood pressure during noradrenaline and phenylephrine infusions, it is possible that the suppressed reflex bradycardia is due to a reduction of the stimulus (i.e. reduced increase in blood pressure).

The suppression of the pressor effect of dopamine by anesthesia is much greater than in phenylephrine-infused rats. This is possibly due to the reduced activation of the alpha-adrenoceptors since it is known that dopamine causes a reduction in blood pressure in animals pre-treated with alpha-adrenoceptor blocking agents[3,4]. In addition, the release of dilator prostaglandins[6] as well as renal, mensenteric and coeliac bed vasodilation[5] would contribute to the depressor effect of dopamine in the anesthetized rats. But whether these actions of anesthesia are centrally or peripherally mediated cannot be ascertained from the results of this study.

It is concluded that pentobarbital-anesthetized rats are unresponsive to the pressor effect of i.v. dopamine which suggests that anesthetization is a determinant of the blood pressure response to dopamine.

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0014-4754/87/080880-04$1.50 + 0.20/0

Histochemical evidence for the presence of dipeptidylpeptidase IV in the Schwann cells of skin unmyelinated axons

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Summary. DPP IV activity was localized in the nerve fascicles of cat glabrous skin at light and electron microscope levels. The observation that the DPP IV end product was restricted to the axon-Schwann cell interface suggests that this enzyme may be involved in the interactions between unmyelinated axons and their Schwann cells.
Key words. Ultrahistochemical localization; dipeptidylpeptidase IV; Schwann cell.

Dipeptidylpeptidase IV (DPP IV) is a serine exopeptidase which removes X-Pro sequences from N-termini of peptides or artificial substrates[1,2]. The histochemical localization of DPP IV has been studied in various tissues[3,4], including peripheral nerve structures[5,6]. The biological role of DPP IV in peripheral nerve structures is obscure. However, the ability of DPP IV to degrade effectively substance P (SP) has been demonstrated biochemically[7,8]. The undecapeptide SP has a widespread distribution in the central and peripheral nervous system[9], including a subpopulation of primary sensory