Hypotensive action of clonidine after adrenalectomy in the rat

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There are many reports showing that clonidine is a centrally acting antihypertensive drug (for review see Van Zwieten, 1975). Its intravenous injection in anaesthetized animals has a biphasic effect on blood pressure, a long lasting decrease follows a short initial rise (Hoefke & Kobinger, 1966). The initial rise is caused, at least in part, by a peripheral mechanism, while the hypotensive action is caused by an effect on the central nervous system. The primary site of action is thought to be mainly on structures of the medulla oblongata-pons (Schmitt, Schmitt & others, 1973; Van Zwieten, 1975). In unanaesthetized rats (Pals, 1975; Trolin, 1975), or in rats anaesthetized with urethane (Ohkusu, 1971) the hypotensive action of clonidine was absent, small or unpredictable. In addition several authors have shown that the drug has an opposing effect on the central nervous system after intravenous (Shaw, Hunyor & Korner, 1971; Trolin, 1975) or central (Bousquet & Guertzenstein, 1973; Philippu, Demmeler & Roensberg, 1974) administration. The opposing effect on the central nervous system probably inhibits the hypotensive action. The present report shows that the adrenal gland has a role in opposing the hypotensive action of intravenous clonidine in conscious and in anaesthetized rats.

Male Wistar rats (Wi/CPB, TNO, Zeist, the Netherlands), 200–250 g, were used. In conscious rats blood pressure and heart rate were measured via an indwelling cannula in the iliac artery (Nijkamp, Ezer & De Jong, 1975). Cannulas were implanted under ether anaesthesia 24 h before the experiment. In rats anaesthetized with urethane (1·3 g kg^{-1}, i.p.) or pentobarbitone (75 mg kg^{-1}, i.p.) the femoral artery was cannulated. In one group the right common carotid artery was used instead of the femoral artery. Blood pressure was recorded using a Statham transducer ($P_{23}AC$) connected to a Grass Polygraph. The jugular vein was cannulated for intravenous injection of clonidine. Each rat received only one injection in a volume of 0·5 ml kg^{-1}. Body temperature was kept at 36–37°. Twenty min before the administration of clonidine bilateral adrenalectomy or a sham operation was performed. Similarly, in the experiments in conscious rats the adrenals were removed under ether anaesthesia.

As shown in Table 1 an injection of clonidine (10 μg kg^{-1}) caused a significant decrease in blood pressure and heart rate in both groups of anaesthetized rats, the effect being more pronounced in rats anaesthetized with pentobarbitone. No significant effect was observed in unanaesthetized rats. In the intact and in the adrenalectomized anaesthetized rats basal values of heart rate were increased by 14-24%, while pentobarbitone slightly increased basal blood pressure. After adrenalectomy, the hypotensive action of clonidine became evident in unanaesthetized rats, and was much more marked in rats anaesthetized with urethane. Bradycardia was observed in both groups becoming as large as 37% in rats anaesthetized with urethane. In contrast, in rats anaesthetized with pentobarbitone, adrenalectomy did not significantly alter either the hypotension, or the bradycardia. Also after a lower dose of clonidine (5 μg kg^{-1}) adrenalectomy failed to affect the decrease in blood pressure and heart rate of rats anaesthetized with pentobarbitone. In none of the groups was a difference in time course observed. The maximal effects occurred 10–20 min after administration of clonidine. Also the initial pressor response (35-45 mm Hg) did not differ between these groups. Administration of vehicle (0·9% NaCl) had no effect on blood pressure and heart rate. In one group of rats, cannulated in a carotid artery and anaesthetized with pentobarbitone, a pronounced hypotensive effect of clonidine was observed. After a dose of 5 μg kg^{-1} the decrease was 51 ± 5 mm Hg (n = 7), compared with 35 ± 6 mm Hg (n = 7) in rats with a femoral cannula. The decrease in blood pressure and heart rate in rats with a carotid cannula was dose dependent (Fig. 1).

The present results show that in intact conscious rats clonidine has no effect on blood pressure and heart rate. Anaesthesia was clearly shown to be important for demonstration of the hypotensive action of clonidine as also indicated in earlier studies (Trolin, 1975, Timmer-

Table 1. *Effect of adrenalectomy on the hypotensive action of clonidine (10 μg kg^{-1}, i.v.) in conscious rats and in rats anaesthetized with urethane or pentobarbitone.*

Data are means ± s.e.m. of 7 rats. Change in blood pressure and heart rate were calculated 15 min after the intravenous administration of clonidine.

	Mean b.p. (mm Hg)	Δ b.p. (mm Hg)	Heart rate beats min^{-1}	Δ heart rate beats min^{-1}
Unanaesthetized				
Sham operation	133 ± 5	− 7 ± 4	357 ± 16	− 0±16
Adrenalectomy	112 ± 7	−22 ± 4*	360 ± 15	−18±24
Urethane				
Sham operation	105 ± 4	−17 ± 4	408 ± 26	−23±18
Adrenalectomy	144 ± 4	−40 ± 5*	444 ± 22	−165±18**
Pentobarbitone				
Sham operation	127 ± 7	−36 ± 6	443 ± 11	−69±9
Adrenalectomy	126 ± 7	−41 ± 7	418 ± 14	−75±22

* $P < 0.01$ compared with the sham operated rats.
** $P < 0.01$.

* Correspondence.

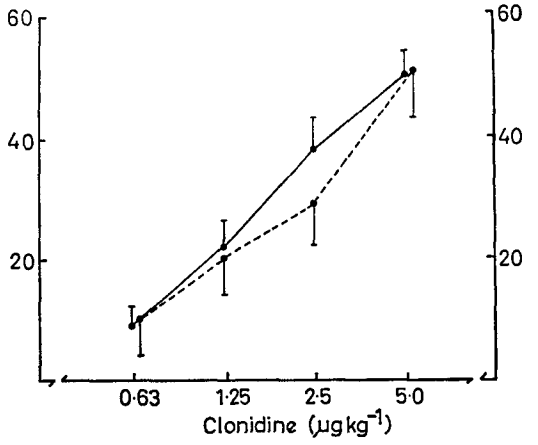

FIG. 1. Decrease in blood pressure (mm Hg) and heart rate (beats min^{-1}) (identical scales) after intravenous administration of different doses of clonidine ($\mu g\ kg^{-1}$) in rats anaesthetized with pentobarbitone. ●——● Blood pressure. ●- - -● Heart rate. Blood pressure was recorded via the right carotid artery. Data are means ± s.e.m. of five rats.

mans, 1976). The effect of anaesthesia may be best explained by a suppression of the blood pressure elevating effect caused by clonidine via the brain (Trolin, 1975). Suprabulbar structures appear to be involved, since in conscious rats (Trolin, 1975) and rabbits (Shaw & others, 1971) clonidine caused a more pronounced decrease in blood pressure after mid-collicular decerebration. It has been suggested by Philippu & others (1974) and Haeusler (1975) that two central adrenergic systems with opposing effects on cardiovascular control may exist. Superfusion of the posterior hypothalamus of urethane-anaesthetized cats with α-adrenergic blocking agents inhibited the pressor response caused by electrical stimulation of this region, while low doses of clonidine enhanced it. On the other hand, superfusion of the region of the nucleus tractus solitarii of the medulla oblongata with α-blocking agents or clonidine had opposite effects on the pressor response of hypothalamic stimulation (Philippu & others, 1974). The hypothalamus is sensitive to anaesthesia, and the rise in blood pressure in rats caused by electrical stimulation of the posterior hypothalamus, which is associated with increased release of adrenal medullary catecholamines and increased sympathetic outflow, is diminished more after barbiturate anaesthesia than after urethane anaesthesia (Buñag & Eferakeya, 1973).

Our data indicate that the adrenal gland has a role in opposing the hypotensive action of clonidine in unanaesthetized rats and in rats anaesthetized with urethane. This may suggest that part of the observed effect of anaesthesia may be explained via inhibition of the release of adrenal catecholamines. However, the involvement of other factors is shown by the fact that after adrenalectomy the effect of clonidine was still less in conscious rats than in rats anaesthetized with urethane or pentobarbitone.

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