than that of (−)-propranolol (Levy et al 1976). With such a selective rate of entry our results are compatible with the two enantiomers having the same potency in the brain.

These results are inconsistent with the anticonvulsant effect being attributable to an action on either β-adrenergic or 5-hydroxytryptaminergic receptors. The membrane stabilizing effect probably accounts for the protective effects of (±)-propranolol.

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Haemodynamic effects of systemic administration of clonidine in the anaesthetized spontaneously hypertensive rat

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The intravenous administration of clonidine produces an initial pressor response followed by a sustained decrease in arterial blood pressure and heart rate in both man and laboratory animals (Kobinger & Walland 1967; Onesti et al 1969). The accompanying changes in regional blood flow have been described for the conscious normotensive monkey by Bolme et al (1975) who reported that blood flow was maintained or increased in the hepatic and renal arteries despite the fall in cardiac output at the expense of the skin, skeletal muscle and brain. Similar observations were made in the same preparation after the administration of α-methyldopa (Forsyth et al 1978) which has been postulated to have a similar action to clonidine on central adrenergic pathways (Fuxe et al 1975). However, in renal hypertensive dogs clonidine produces decreases in blood flow through the splanchnic and femoral arteries as well as to the heart, brain and kidneys (Laubie & Schmitt 1969). Unfortunately, no comparison of the actions of clonidine in normotensive and hypertensive animals has been made in the same species so it is not possible to determine whether the differences in the actions of clonidine are due to species or hypertension. Since Hiley & Yates (1978) have observed different resting patterns of cardiac output distribution in anaesthetized spontaneously hypertensive rats (SHR) relative to normotensive Wistar controls (NR), it is important to establish whether the actions of clonidine on regional blood flow are different in hypertension. Accordingly we have compared the haemodynamic effects of intravenous clonidine in these two strains of rat.

Groups of age-matched male normotensive rats from our own colony and Okamoto strain spontaneously hypertensive rats (OLAC 1976, Ltd, Bicester, Oxfordshire) were anaesthetized with ketamine (120 mg kg^{-1} i.p.).

The right carotid artery was cannulated and, with the aid of pressure monitoring, the tip of the cannula was manipulated into the left ventricle. 60 000–80 000 carbonized plastic microspheres (15 ± 5 μm) labelled with ^{141}Ce (3M Co., St Paul, Minnesota, U.S.A.) and suspended by ultrasonication in 0·6 ml 0·9% NaCl containing 0·02% Tween 80 were injected through the left ventricular cannula over 20 s. Simultaneously, and for 70 s after injection, blood was withdrawn from a femoral artery with a syringe withdrawal pump (Perfusor IV, Braun, Melsungen, Germany). Arterial blood pressure was recorded from the other femoral artery by means of a pressure transducer (Bell and Howell type 4–422–0001) and a pen recorder (Grass Model 79 polygraph). A fourth cannula was placed in the right femoral vein. The injection of microspheres was made 15–20 min after intravenous administration over 30 s of either clonidine (20 μg kg^{-1}) or 0·3 ml

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of 0·9% NaCl. This was found to be the time when clonidine produced its maximum depressor response.

The animal was killed with an overdose of pentobarbitone and the tissue samples or organs were dissected out and placed in 27 mm diameter scintillation vials for radioactivity counting in a well-type gamma counter (Intertechnique Model CG 4000 with a 75 mm crystal). Cardiac output, its distribution and tissue blood flow were determined by the method of McDevitt & Nies (1976). Statistical comparisons were made by the Wilcoxon ranking test.

Clonidine hydrochloride (the gift of Boehringer Ingelheim) was made up in 0·9% NaCl (20 μg ml^{-1}).

After an initial pressor response the administration of clonidine produced significant falls in mean arterial blood pressure and cardiac output in both NR and SHR with no significant change in total peripheral resistance (Table 1). The maximum fall in blood pressure occurred in both strains of rat 15–20 min after the injection of clonidine and this was selected as the time to inject the microspheres. Before the administration of clonidine there was no significant difference in arterial blood pressure between the saline- and clonidine-treated animals in each strain.

Clonidine produced a significant reduction in the distribution of cardiac output to the heart of both SHR and NR and, in addition, the lungs of SHR also received a decreased fraction of cardiac output after the drug. The hepatic artery of NR received an increased proportion of cardiac output such that blood flow (ml min^{-1} g^{-1} liver) was also significantly increased. The kidneys of both strains received an increased fraction of cardiac output after clonidine with the result that, despite the fall in cardiac output, renal blood flow was maintained in SHR. However, it was significantly decreased in NR. Further changes in cardiac output distribution produced by clonidine were a decrease to the brain of SHR and, in NR, an increase to the hepato-splanchnic tissues which reflects the total fraction of cardiac output received by the liver. Clonidine also produced a decrease in the proportion of cardiac output received by each gram of skeletal muscle in NR.

Since total peripheral resistance was unchanged by clonidine in both NR and SHR, the hypotensive effect it produced must have been solely the result of the diminished cardiac output. In this respect our findings confirm those previously reported by other workers in both animals and man (Vorburger et al 1968; Maxwell 1969).

This reduction in cardiac output will cause a proportionate fall in blood flow through those organs or

Table 1. The effect of intravenous clonidine (20 μg kg^{-1}) on cardiac output and its distribution in normotensive and spontaneously hypertensive rats

	NR Saline (n = 7)	NR Clonidine (n = 7)	SHR Saline (n = 7)	SHR Clonidine (n = 7)
Body weight (g)	335 ± 15	340 ± 18	296 ± 14	290 ± 13
[a]Mean arterial pressure (mm Hg)	112 ± 5	69 ± 3**	178 ± 7	91 ± 3**
[b]Fall in mean arterial pressure (mm Hg)	—	40 ± 5	—	82 ± 6
Cardiac output (ml min^{-1} per 100 g bw)	20·6 ± 1·3	12·9 ± 1·0**	21·0 ± 0·8	11·7 ± 0·7**
Total peripheral resistance (mm Hg ml^{-1} min 100 g bw)	5·7 ± 0·2	5·4 ± 0·5	8·2 ± 0·6	7·5 ± 0·7
% Cardiac output				
Heart	5·8 ± 0·4	4·4 ± 0·4*	6·5 ± 0·5	4·2 ± 0·4**
[c]Lungs	3·1 ± 0·5	3·0 ± 0·6	4·1 ± 0·4	2·4 ± 0·3**
[d]Liver	1·9 ± 0·3	4·8 ± 0·3**	6·0 ± 0·4	7·0 ± 0·6
Spleen	1·3 ± 0·2	1·7 ± 0·2	1·1 ± 0·05	1·2 ± 0·1
Kidneys	19·5 ± 0·9	24·1 ± 1·2*	17·6 ± 0·6	30·3 ± 2·0**
Brain	3·5 ± 0·3	3·7 ± 0·3	4·2 ± 0·2	3·0 ± 0·2*
Gastrointestinal tract + pancreas	17·5 ± 1·1	18·7 ± 1·3	11·6 ± 0·6	13·3 ± 0·6
[e]Hepatosplanchnic	20·9 ± 1·6	26·5 ± 1·5*	19·2 ± 1·3	21·5 ± 1·3
Total of organs investigated	52·7 ± 1·7	58·2 ± 2·3	50·5 ± 2·1	60·0 ± 3·7*
% Cardiac output g^{-1}				
Skin	0·13 ± 0·008	0·13 ± 0·01	0·08 ± 0·007	0·09 ± 0·006
Skeletal muscle (forelimb)	0·33 ± 0·03	0·19 ± 0·02**	0·17 ± 0·02	0·16 ± 0·01
Blood flow (ml min^{-1} g^{-1})				
[d]Liver	0·11 ± 0·008	0·16 ± 0·015*	0·30 ± 0·02	0·19 ± 0·015**
Kidneys	5·4 ± 0·3	3·1 ± 0·2**	4·6 ± 0·2	4·8 ± 0·3

All values given as mean ± s.e.m. Statistical significance from saline injected animals. *$P < 0.05$ **$P < 0.01$

[a] at the time of microsphere injection

[b] produced by administration of clonidine

[c] bronchial circulation and arterio-venous shunting

[d] hepatic artery

[e] hepatic artery, spleen, gastrointestinal tract and pancreas.

tissues which receive the same fraction of cardiac output after the administration of clonidine as they did before the drug. However, it is clear from the data presented here that the resistance to blood flow must change in certain tissues, despite total peripheral resistance being unchanged, since the pattern of cardiac output distribution is changed by clonidine in both strains of rat.

Thus, in NR the fractions of cardiac output passing to the kidneys and hepatic artery are increased whilst there are decreases to the heart and in skeletal muscle blood flow. These changes are similar to those reported for the normotensive monkey (Bolme et al 1975) although, in that animal, no change was reported in the fraction of cardiac output passing to the heart, and skin blood flow was reduced. In SHR, clonidine also produced increases in cardiac output distribution to the kidneys and hepatic artery but, although renal blood flow was maintained at pre-clonidine values hepatic arterial flow was decreased. This is in contrast to the significantly greater hepatic arterial flow produced by clonidine in NR.

As a result of the hypertension in SHR there is an increased wall thickness of the resistance vessels in all the systemic vascular beds (Folkow et al 1970a, b). This results in an increased wall/lumen ratio and consequently the systemic vascular bed when considered as a whole in SHR exhibits a raised flow resistance even during maximal dilation compared to NR (Folkow et al 1970a, b). However, the adaptation of the renal vascular bed to increased pressure in SHR differs from other vascular beds in that at maximal dilation renal resistance is lower than in NR (Folkow et al 1971). This appears to be a result of an increase in lumen diameter as well as an increase in vessel wall thickness in the renal vessels of SHR (Folkow et al 1971). As a consequence at low perfusion pressures there may be a lower renal resistance in SHR than NR. The hypotension produced by clonidine may sufficiently lower the perfusion pressure to the kidneys in SHR such that renal resistance is lower than in NR enabling renal blood flow to be maintained in SHR in contrast to NR. This implies that the effects of clonidine on renal blood flow are a local response of the vessels to its hypotensive action and not a result of a central action or a direct effect on the kidney. Indeed in a later study of the isolated renal vascular bed of SHR Folkow et al (1977) concluded that the renal vascular smooth muscle of SHR may adjust blood flow and glomerular filtration rate even better than in NR. The conclusions drawn by Folkow et al about the isolated perfused kidney provide an explanation for the differences in renal blood flow changes seen in the intact normotensive and hypertensive animal after the administration of the antihypertensive drug clonidine.

Since the hepatic artery receives 6% of the cardiac output in untreated anaesthetized SHR and clonidine decreases cardiac output by 44%, in order to maintain hepatic arterial flow after clonidine the artery would have to receive more than 10% of the available cardiac output. The fact that this is not achieved suggests that the reorganization of cardiac output it would require may be impossible in the rat or that the ability to respond is limited by resistance factors as discussed above.

Another contrast to NR is that, in SHR, the total fraction of cardiac output received by the organs investigated was significantly greater after clonidine. Since total peripheral resistance is unchanged this indicates that, in SHR, other tissues not studied must have suffered a reduction in their share of the cardiac output.

The results show that clonidine-induced regional blood flow changes in the spontaneously hypertensive rat differ in several respects from those occurring in the closely related normotensive Wistar rat and that these differences may be a result of the adaptive vascular changes occurring in hypertension.

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