On the other hand, the ID_{50} values of amplitude show that β-receptors are much more sensitive to temperature change than α-receptors. Furthermore, the shift of ID_{50} value of amplitude due to the elevation of temperature was much larger than that of pD_2 value in the presence of PH, whereas the former was smaller than the latter in the presence of PR. These observations suggest that the main areas of adrenoceptors which mediate the relaxation may be different from those which mediate the amplitude inhibition.

PR significantly inhibited the relaxation caused by NA at 25, 30 and 37 °C; however, PH did not affect it significantly at any temperature. This shows that the relaxation of rabbit jejunum by NA is mainly mediated via adrenergic β-receptors at each of the temperatures. PH significantly inhibited the amplitude inhibition by NA at 30 and 37 °C, and at 25 °C though insignificantly. The amplitude inhibition by NA was also inhibited by PR at 25 and 30 °C, whereas it was augmented at 37 °C. This demonstrates that the amplitude inhibition by NA is mediated via α-receptors at 37 °C, and not only α- but also β-receptors at 30 and 25 °C.

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The effect of age on cardiac output and its distribution in the rat[1]

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Summary. Cardiac output distribution in the rat was found to be affected by age. Cardiac index and blood flow to the liver, kidneys, skin and skeletal muscle were lower in 11–12 month compared to 3–4 month old rats.

Liver and renal blood flow are especially important in the kinetics of drug disposition[2-5] but little information is available concerning the effect of ageing on these haemodynamic parameters in the rat. Also the overall pattern of distribution of cardiac output may be affected by age and this may interfere with or enhance the ability of a drug to reach its site of action. Since toxicological studies are routinely performed in rats of different ages[6] any haemodynamic differences may be of great relevance. In this paper we present an analysis of haemodynamic patterns determined by the radioactive microsphere technique in young adult (3–4 months) and middle-aged (11–12 months) rats.

Method. Male Wistar rats of either 3–4 months (325–400 g) or 11–12 months (575–625 g) 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 diameter; 3 M Company, St. Paul, Minn.) labelled with ^{85}Sr were injected into the left ventricle over 20 sec in a total volume of 0.6 ml 0.9% saline/0.02% Tween 80. Simultaneously, blood was withdrawn from a femoral artery at 0.6 ml min^{-1} for 90 sec by means of a syringe withdrawal pump (Perfusor IV, Braun, Melsungen, FRG). Arterial blood pressure was recorded from the other femoral artery by means of a pressure transducer (Bell & Howell type 4-422-0001) and a pen recorder (Grass Model 79).

Cardiac output, its distribution and tissue blood flow were determined by the method of McDevitt and Nies[7]. In this method hepatic arterial flow is determined from the microspheres trapped in the liver and portal venous return is obtained indirectly by adding together the flows to the spleen, pancreas and gastrointestinal tract. Throughout this paper, liver blood flow refers to the sum of hepatic arterial and portal venous flow, i.e. blood flow through the hepatosplanchnic tissues. Statistical comparisons were performed by means of a non-paired Student's t-test.

Results. Cardiac output, its distribution and tissue blood flow for the 2 groups of rats are shown in the table. Although cardiac output was the same for both young adult and middle-aged rats, cardiac index (ml min^{-1} kg^{-1}) was significantly lower in the older rats owing to their greater body weight. The pattern of distribution of cardiac output also differed in that, when compared to young adult rats, middle-aged animals showed reductions of 27, 55 and 46% respectively in the proportions of cardiac output received by the kidneys, gastrointestinal tract and hepatosplanchnic tissues. However, middle-aged rats showed a 55% increase in the apparent fraction of cardiac output reaching the lungs.

Blood flow through skin and skeletal muscle in middle-aged rats was approximately 55% lower compared to young adult animals. The blood flow through the hepatic artery relative to liver weight was 31% lower in middle-aged rats whilst total liver blood flow (hepatosplanchnic) relative to body weight or liver weight was approximately 60% lower. A 47% lower renal blood flow was also detected in the middle-aged animals.

Discussion. The fact that cardiac index is lower in middle-aged rats than it is in the younger animals is of primary importance since, even if the patterns of cardiac output distribution were similar, any change in organ or tissue mass in the older animals will produce a corresponding alteration in tissue blood flow. Thus those organs and tissues which increase in size and give the greater overall body weight will have a lower rate of perfusion if they merely continue to receive the same fraction of cardiac output. This may be the explanation for the lower blood flows in skin and skeletal muscle found in the middle-aged rats, since cardiac index in these animals is 41% lower than

Cardiac output, its distribution and tissue blood flow in young adult and middle-aged rats

	Young adult rats 3-4 months (n = 10)	Middle-aged rats 11-12 months (n = 10)
Body weight (g)	365 ±21	608 ±17***
Mean arterial pressure (mmHg)	121 ± 4	122 ± 5
Cardiac output (ml min^{-1})	75.0 ± 6.0	75.6 ± 6.7
Cardiac index (ml min^{-1} kg^{-1})	210 ±20	123 ±11***
Cardiac output (%)		
Heart	7.0 ± 1.0	8.1 ± 1.4
Lungs[a]	4.5 ± 0.8	7.0 ± 0.9*
Liver[b]	2.7 ± 0.6	2.4 ± 0.4
Spleen	1.2 ± 0.3	1.1 ± 0.3
Kidneys	19.8 ± 1.6	14.4 ± 1.3*
Epididymides	0.20± 0.01	0.19± 0.02
Testes	1.0 ± 0.1	1.0 ± 0.1
Brain	3.9 ± 0.5	4.5 ± 0.4
Gastrointestinal tract and pancreas	17.3 ± 1.7	7.8 ± 0.9***
Hepatosplanchnic[c]	21.1 ± 2.2	11.4 ± 1.3**
Blood flow (ml min^{-1} g^{-1})		
Skin	0.08± 0.01	0.04± 0.005**
Skeletal muscle (fore limb)	0.23± 0.03	0.09± 0.016**
Heart	4.26± 0.54	3.74± 0.82
Liver[b]	0.13± 0.02	0.09± 0.01*
Kidneys	5.7 ± 0.4	3.0 ± 0.4***
Hepatosplanchnic[c]	1.1 ± 0.1	0.44± 0.03**
Blood flow (ml min^{-1} 100 g b.wt^{-1})		
Hepatosplanchnic[c]	4.2 ± 0.3	1.5 ± 0.3***

All values are given as mean ±SEM. *$p<0.05$; **$p<0.01$; ***$p<0.001$. [a]Bronchial circulation and arterio-venous shunting. [b]Hepatic artery. [c]Hepatic artery, spleen, pancreas and gastrointestinal tract.

the young adult animals and the perfusion of skin and muscle respectively are 50% and 61% lower. However, it is possible that the greater changes in perfusion of these tissues are the result of their receiving a lower proportion of cardiac output. Certainly this is an important factor in the decreased blood flow through the kidneys and the gastrointestinal tract. Thus, the kidneys received 27% less of the cardiac output in the middle-aged rats and blood flow was 47% lower whilst for the gastrointestinal tract blood flow was 74% lower with it receiving 55% less of the cardiac output. Since the splanchnic flow was also accompanied by a decreased flow in the hepatic artery, total liver blood flow was markedly lower in the older animals. This will undoubtedly interfere with the ability of the liver to deal with endogenous and exogenous compounds[5] and the change in renal blood flow may also have important consequences for the elimination of drugs and their metabolites.

Cardiac output and its distribution may be affected by anaesthesia itself and by the agent used[8-10]. The decreased blood flows in the gastrointestinal tract and kidneys in middle-aged rats could be due to circulating catecholamines or increased activity in the sympathetic nervous system and ketamine has been reported to produce hypertension and tachycardia in man. However, these actions in man are thought to be the result of interaction with central cardiovascular centres[11]. Also, Bell et al.[8] did not find any evidence for increased activity of catecholamines or the sympathetic nervous system when cardiac output distribution under ketamine anaesthesia was compared with that found with pentobarbitone or alphadolone/alphaxalone anaesthesia. In contrast, ethyl carbamate anaesthesia did produce a pattern of distribution of cardiac output which was suggestive of excess catecholamines.

Thus, if ketamine induced increases in catecholamine activity or sympathetic nervous activity are the cause of the different cardiac output distribution in the middle-aged rats, the effect must be restricted to the older animals.

Another observation of interest is the apparent increase in the percentage of cardiac output received by the lungs in the middle-aged relative to the young adult rats. The microspheres trapped in the lungs are those which pass through systemic arterio-venous anastomoses as well as those reaching the lung through the bronchial circulation. Thus it is possible that there is increased arterio-venous shunting in the older animals rather than, or as well as, an increase in bronchial circulation.

It can be seen from the data presented here that there may be considerable differences in drug disposition and pharmacokinetics in rats of different ages. Such possibilities must be considered when comparing information from rats of varying ages.

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