Influences of temperature change on the relaxation and amplitude inhibition by noradrenaline in the rabbit jejunum

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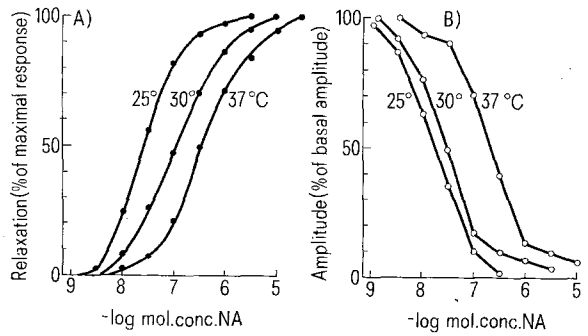
Summary. In the rabbit jejunum, the elevation of temperature within the range of 25–37 °C diminished the sensitivity to noradrenaline (NA) for both the relaxation and amplitude inhibition. The relaxation by NA was mainly mediated via adrenergic β-receptors at 25, 30 or 37 °C. The amplitude inhibition was mediated via α-receptors at 37 °C, and both α- and β-receptors at 30 or 25 °C.

In the rabbit papillary muscles, the sensitivities of adrenoceptors are depressed by the elevation of temperature, and the sensitivity of α-receptors is depressed more than that of β-receptors[1]. In the spontaneously-beating rat atria, the sensitivity of adrenoceptors to isoproterenol is lower, and that of adrenoceptors to phenylephrine higher, at 17 °C than at 31 °C for both the inotropic and chronotropic responses[2]. In the rabbit ileum, the sensitivity of α-receptors is not altered by the elevation of temperature, whereas that of β-receptors is depressed[3,4]. Cooling from 37 to 29 or 24 °C augments not only the contraction evoked by noradrenaline[5] but also relaxation by isoproterenol[6] in isolated saphenous veins of the dog. Thus, the sensitivity changes of adrenoceptors due to a temperature change are not in the same direction in all preparations.

In this study, the influences of temperature change on the relaxing and amplitude-inhibiting effects of noradrenaline on the rabbit jejunum were further investigated, focusing attention on the sensitivities and pharmacological characteristics of adrenoceptors.

Methods and materials. Jejunal segments of male rabbits about 1.5 cm in length were suspended in a bath containing 20 ml of Tyrode solution bubbled with O_2 gas. The isotonic responses at 0.8 g tension were recorded on a kymograph. The relaxing and amplitude-inhibiting effects of noradrenaline (NA) at 25, 30 and 37 °C were investigated, the drug administered cumulatively. The influences of phentolamine (PH, 10^{-5} M) and propranolol (PR, 10^{-6} M) on these effects were also studied. The pD_2 value[7] was calculated from the relaxation. Further, the negative logarithm of NA molar concentration reducing the amplitude to 50% of the basal (ID_{50} value of amplitude) was calculated. Significant differences were calculated by means of Student's t-test.

Results. NA elicited the dose-related relaxation and amplitude inhibition of jejunum at 25, 30 and 37 °C. The elevation of temperature from 25–30, and further to 37 °C, shifted the dose-response curve of NA to the right in a parallel fashion for both the relaxation and the amplitude inhibition (figure). In the presence of PH or PR, the dose-response curve for the relaxation also shifted to the right.



Influences of temperature change on the log dose-response curves of noradrenaline for relaxation (A) and amplitude inhibition (B).

The pD_2 value was significantly reduced by the elevation of temperature (table, A, control). The pD_2 value in the presence of PH or PR – a value indicating the affinity of NA to the adrenergic β- or α-receptors – was significantly smaller at 37 and 30 than at 30 and 25 °C, respectively. PR decreased the pD_2 value of NA significantly at each temperature (from 7.54 to 7.09 at 25 °C, from 6.86 to 6.32 at 30 °C and from 6.46 to 5.90 at 37 °C), whereas PH did not affect it significantly.

As shown in the table, B, the ID_{50} value of amplitude was significantly smaller at 37 °C (6.67) than at 30 or 25 °C (7.56 or 7.80). PH decreased the ID_{50} value of amplitude significantly at 30 °C (from 7.56 to 6.22) and at 37 °C (from 6.67 to 4.55), and showed a tendency to decrease it at 25 °C (from 7.80 to 7.42, $0.05 < p < 0.1$). PR decreased the ID_{50} value of amplitude at 25 °C (from 7.80 to 7.37) and 30 °C (from 7.56 to 7.15), but increased it at 37 °C (from 6.67 to 6.91).

Discussion. In the presence of PH or PR, the elevation of temperature shifted the dose-response curve of NA for relaxation to the right in a parallel fashion and reduced the pD_2 value significantly. Also, temperature elevation decreased the ID_{50} value of amplitude more in the presence of PH than in the presence of PR, when the shift was very small. The changes in the pD_2 value suggest that the elevation of temperature decreases the affinity of NA in a same degree both to the adrenergic α- and β-receptors of rabbit jejunum, and that the affinity to α-receptors is smaller than that to β-receptors at the same temperature.

The pD_2 value for noradrenaline calculated from segment relaxation (A) and the negative logarithm of the molar concentration of the drug reducing the amplitude to 50% of the basal (B)

	Control	Phentolamine	Propanolol
A			
25 °C	7.54±0.11 (8)	7.29±0.17 (6)	7.09±0.35 (5)[b]
30 °C	6.86±0.09 (7)[a]	6.76±0.03 (5)[a]	6.32±0.20 (5)[a,b]
37 °C	6.46±0.13 (7)[a]	6.40±0.16 (5)[a]	5.90±0.14 (5)[a,b]
B			
25 °C	7.80±0.14 (7)	7.42±0.09 (7)	7.37±0.23 (5)[b]
30 °C	7.56±0.09 (10)	6.22±0.22 (8)[a,b]	7.15±0.22 (5)[b]
37 °C	6.67±0.08 (12)[a]	4.55±0.22 (5)[a,b]	6.91±0.23 (6)[c]

[a]Significant difference in comparison with the lower temperature ($p < 0.05$). [b]Significant difference in comparison with the control value at the same temperature ($p < 0.05$). [c]Significant increase in comparison with the control value at the same temperature ($p < 0.05$). Control, noradrenaline alone; Phentolamine, phentolamine (10^{-5} M)+noradrenaline; Propranolol, propranolol (10^{-6} M)+noradrenaline. Number of experiments in parentheses. Values are means ± SE.

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