α-Adrenoceptor alteration by alloxan diabetes in iris dilator muscle of the rabbit

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Summary. Alloxan diabetes promotes, in the rabbit, decrease in sensitivity to norepinephrine (NOR) in the isolated iris dilator muscle at 25 and 37 °C in vitro.

In previous work, Matheny and Ahlquist have demonstrated the presence of alpha and beta receptors in iris dilator muscle of the rabbit[2]. In this same paper, they have demonstrated that alpha receptors are more responsive to NOR at 29 °C than at 37 °C. This fact has also been demonstrated by Fonteles and Karow[3] in the isolated rabbit kidney, perfused at 37 and 25 °C. Recently, Tirri and Siltuvuori have demonstrated lowered responses to NOR and phenylephrine of femoral artery of rats which were submitted to cold acclimatisation[4]. Changes in sensitivity of adrenergic receptors to cold have been attributed to modification of the metabolic environment[5]. In the present work, we have tested this hypothesis in a condition were metabolism is generally altered[6].

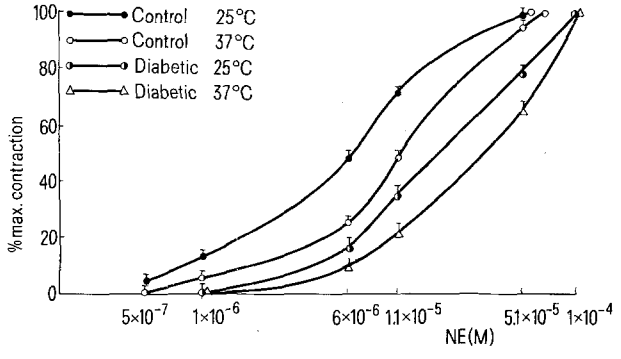
Material and methods. Rabbits (2-3 kg) were made diabetic by i.v. injection of alloxan (150 mg/kg), and after 2-3 weeks, the animals were killed by a blow on the head, exsanguinated and the eyes enucleated. Strips of the iris dilator muscle of 2 mm width were isolated from each eye by the method of Kern[7]. The strips were then mounted in a 25-ml bath containing balanced salt solution (BSS) of the following composition (mM): NaCl, 141.58; KCl, 5.40; $NaHCO_3$, 15.00; glucose, 11.00; NaH_2PO_4, 0.40; and $CaCl_2$, 2.10. The solution was aerated with a mixture of 97% oxygen and 3% carbon dioxide and the pH adjusted to 7.4 when necessary. Recordings were made of tension change on a Beckman type R411 recorder at sensitivity of 1 mg/0.5 mm. Resting tension was maintained at 100 mg. Temperature was kept constant using a Haake heater-circulator. During temperature changes, the preparation was allowed to equilibrate for at least 1 h. BSS was changed in the chambers each 15 min during the equilibration period.

Dose x response curves were plotted according to classical procedures, for iris muscle of diabetic and control animals. Blood glucose determinations were made by the glucose oxidase method[8]. The rabbits were considered diabetic when fasting blood glucose was above 200 mg%.

Results and discussions. The table and figure 1 show the log-dose-response curves and the data of changes in tension of diabetic and control animals at 25 and 37 °C. As in controls, diabetic iris dilator muscle have shown greater sensitivity to low NOR at 25 °C, but at both temperatures, larger drug concentration is required to obtain the same effects, which tends to shift the dose-concentration-response curve to the right. This difference of response of the preparation is significant at the level of $p < 0.01$. The importance of this is related to its earlier appearance, since it can be seen in animals made diabetic for only 1 week.

Diabetic-induced changes in vascular reactivity to drugs have been demonstrated in animals[9] and man[6]. However this is the first report relating loss of receptor sensitivity in the iris muscle and diabetes. Diabetic retinopathy is well established as a medical entity. However, we believe these changes are related solely to metabolic alterations due to the lack of insulin or to hyperglycemia, which fits the concept forwarded by Kunos et al.[10], that the metabolic environment regulates adrenergic receptor quality.

In 1964, Brody and Dixon[11] found an increase in vascular reactivity to NOR, epinephrine and angiotensin II in the perfused hindquarters of rats made diabetic by alloxan. This has been confirmed by the work of Cseuz et al.[9]. However, Costa e Forti and Fonteles[12] have found in the rabbit kidney a lack of responsiveness to NOR during the first min of drug infusion. Christlieb et al., 1975[13], have found that the increase in vascular reactivity to NOR and angiotensin II in humans is related to the degree of retinopathy[12]. The importance of the adrenoceptor alteration by disease has been emphasized by Ahlquist[14] recently.



Effects of norepinephrine on isolated iris dilator muscle of control and alloxan treated rabbits

NE concentration (M)	Control (n = 24) 25 °C	37 °C	Diabetic (n = 12) 25 °C	37 °C
5×10^{-7}	05.1 ± 1.6	0.2 ± 1.1	0	0
1×10^{-6}	13.4 ± 2.1	6.3 ± 1.6	0.27 ± 0.27	0.5 ± 0.5
6×10^{-6}	48.3 ± 2.7	24.1 ± 2.1	16.10 ± 3.90	9.9 ± 2.5
1.1×10^{-5}	71.2 ± 1.9	49.4 ± 2.4	34.70 ± 5.40	21.6 ± 3.7
5.1×10^{-5}	99.0 ± 2.6	94.9 ± 2.0	77.90 ± 3.30	65.2 ± 3.4
1×10^{-4}	100	100	100	100

Data shown as 90 maximal concentrations ± SE.

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