Influence of Diazoxide on Regional Blood Flow in Rats

Diazoxide (7-chloro-3-methyl-1, 2, 4-benzothiadiazine, 1, 1-dioxide) is one of the most potent hypotensive agents known up to the present. The fall of the blood pressure after diazoxide is due to a decrease of the total peripheral vascular resistance[1–5]. The influence of diazoxide on local blood flow was investigated in only a few cases. Increased blood flow has been found through the coronary vascular bed[1,4] and through one extremity[4], and reports on the effect on renal blood flow differ[4,6,7].

Experiments were therefore undertaken to investigate whether the peripheral distribution of the cardiac output in rats is influenced by diazoxide. The tissue uptake of radioactive indicator ^{86}Rb according to SAPIRSTEIN[8] was used for this purpose.

Method. Male Wistar rats weighing 150–175 g fed standard laboratory diet (Larsen) and water ad libitum were used in all experiments. Tissue uptake of ^{86}Rb in conscious rats was estimated by means of SAPIRSTEIN's method in a modification elaborated in this laboratory[9]. A dose of 10 μCi ^{86}Rb (Institute of Nuclear Research, Řež, Prague) in 0.5 ml of physiological saline was injected quickly into the tail vein. Forty seconds after the application of the isotope the animals were sacrificed by decapitation. Immediately after bleeding, organs and tissue samples were dissected as follows: heart, lung, sample of thigh muscles, kidney, liver, spleen, pancreas, aboral part of the large intestine, pituitary, adrenals, thyroid, sample of perirenal fat and sample of the skin from the ventral side of the body. Small organs were weighed and taken in toto; from larger organs samples weighing about 300–500 mg were taken. Tissues were homogenized by boiling in 3 ml of 10% NaOH. Radioactivity of samples in tubes and of the standard of ^{86}Rb, prepared by an adequate dilution of the dose, were measured under standard conditions in a well-type scintillation counter. Results were expressed in % of the dose in 1 g of the tissue.

Diazoxide (Hyperstat Schering) was injected through the same needle as ^{86}Rb in the tail vein in the dose of 5 mg (0.33 ml of original solution) within 30 sec. (We are grateful to Schering Comp., Bloomfield, New Jersey for kindly supplying the diazoxide.)

Blood pressure was measured directly by means of the carotid artery cannulation.

Results and discussion. Tissue uptake of ^{86}Rb was estimated at 3 different time intervals after the application of diazoxide. ^{86}Rb was injected in groups I, II and III at 5, 90 and 150 sec intervals after the end of a 30 sec lasting application of diazoxide, respectively. The results are presented in the Table and the Figure.

The regional blood flow, indicated by ^{86}Rb uptake, is influenced by diazoxide significantly only in a few organs (as demonstrated by no overlapping of 95% confidence intervals). In the spleen, it falls immediately after the application of diazoxide to 40% of the control values; within 150 sec it approaches the control level. In the heart, it increases progressively to the maximum 128% of control values in 150 sec. In the thyroid gland, it increases in all 3 time intervals, with the maximum of 139% of the control values in 90 sec. In other organs and tissues, no apparent changes were found.

In a control experiment (rats sacrificed 20 and 40 sec after the injection of ^{86}Rb), the validity of the rubidium method in diazoxide-treated animals could be demonstrated. Another control experiment excluded a possible

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Influence of the i.v. injection of 5 mg of diazoxide on local blood flow in rats, as indicated by the tissue uptake of radioactive rubidium ^{86}Rb. Mean values and 95% confidence intervals are presented in 4 groups: controls, application of diazoxide at 5, 90 and 150 sec intervals before ^{86}Rb uptake determination

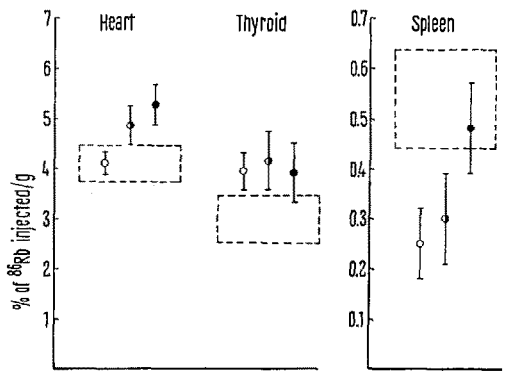
Organ	^{86}Rb uptake in % dose/g											
	Controls			Diazoxide 5 sec			Diazoxide 90 sec			Diazoxide 150 sec		
	No.	mean	95% confidence intervals	No.	mean	95% confidence intervals	No.	mean	95% confidence intervals	No.	mean	95% confidence intervals
Heart	14	4.10	3.76–4.44	14	4.08	3.88–4.28	14	4.85	4.45–5.25	12	5.27	4.86–5.68
Muscle	14	0.51	0.44–0.58	14	0.49	0.45–0.53	12	0.44	0.39–0.49	12	0.47	0.43–0.51
Lung	8	1.81	1.60–2.02	8	1.83	1.55–2.11	7	1.86	1.64–2.08	–	–	–
Kidney	14	7.32	6.32–8.32	14	6.92	6.22–7.62	13	6.63	5.63–7.63	12	6.50	5.85–7.15
Liver	8	0.40	0.29–0.51	8	0.40	0.33–0.47	8	0.52	0.33–0.71	–	–	–
Spleen	14	0.54	0.44–0.64	14	0.25	0.18–0.32	14	0.30	0.21–0.39	12	0.48	0.39–0.57
Pancreas	6	1.20	0.87–1.53	6	1.14	0.88–1.40	6	1.01	0.67–1.35	12	1.05	0.94–1.16
Intestine	14	1.28	1.06–1.50	14	1.09	0.83–1.35	14	1.03	0.68–1.38	12	1.47	1.16–1.78
Pituitary	13	2.98	2.01–3.95	13	2.90	2.49–3.31	14	2.63	2.31–2.95	11	3.07	2.71–3.43
Adrenals	14	2.98	2.49–3.47	14	3.04	2.78–3.30	14	3.32	2.87–3.77	12	3.42	2.96–3.88
Thyroid	14	3.00	2.53–3.47	13	3.96	3.59–4.33	13	4.17	3.59–4.75	12	3.92	3.32–4.52
Fat	8	0.13	0.08–0.18	8	0.11	0.05–0.17	8	0.15	0.07–0.23	–	–	–
Skin	8	0.32	0.25–0.39	7	0.31	0.25–0.37	8	0.31	0.24–0.38			

non-specific effect of the highly alkaline solution (pH 11.6) of diazoxide.

The effect of 5 mg diazoxide, injected i.v. within 30 sec, on blood pressure was determined in 5 rats. Ten seconds after starting the application the blood pressure fell rapidly, within 60 sec it reached minimum values (50% of control values), 5 min after the application the blood pressure was still considerably decreased (65% of control values).

The fall of the blood flow through the spleen is probably due to the contraction of this organ, caused by a rapid decline of the blood pressure[10]. The increase of the blood flow through the heart is consistent with the results of other authors[1,4]. Of interest is the increase in the thyroid gland, which has not been reported before. It is noteworthy that, as we were able to show, the 4 h uptake of radioactive iodine ^{131}I in the thyroid gland of rats is, after 5 mg of diazoxide, significantly inhibited[11]. The blood flow through the pancreas, the secretory function of which is supposed to be influenced by diazoxide[12], remains unchanged.

From the results presented it is possible to conclude that the immediate vascular effect of diazoxide is not the same in all vascular beds. The blood flow increases, in comparison with other organs, markedly only in the heart and thyroid.



Changes in local blood flow in the heart, thyroid gland and spleen of rats after i.v. injection of 5 mg of diazoxide. Mean values of the tissue uptake of ^{86}Rb expressed in % of injected dose/g of the tissue at the following time intervals between diazoxide and Rb uptake determination: ○ 5 sec, ◑ 90 sec, ● 150 sec. Verticals: 95% confidence intervals. Dashed lines: 95% confidence intervals of the control mean values.

Zusammenfassung. Der Einfluss von Diazoxid auf die Organdurchblutung der Ratten wurde mittels ^{86}Rb untersucht. Eine signifikante Durchblutungssteigerung des Herzens (128% der Kontrollwerte) und der Schilddrüse (139%) konnte bis 150 sec nach i.v. Injektion von 5 mg Diazoxid nachgewiesen werden. Die Durchblutung der Milz hingegen sank rasch auf 45% der Kontrollwerte, wobei nach 150 sec Normalisierung eintrat.

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The Effect of Adrenaline on Different States of Sleep

It has been known that adrenaline, injected into the carotid artery, or the subarachnoidal space, or the lateral ventricle of the cat, produces 'anaesthesia-like' or 'sleep-like' effects[1-3]. Data about adrenaline influence on the quantity and quality of sleep, especially its paradoxical phase, are still missing. Therefore, the aim of this study was to investigate the effect of adrenaline on slow wave and paradoxical sleep.

Six adult cats (2.6–3.2 kg) were stereotaxically implanted with cortical monopolar and deep bipolar electrodes. Permanent cannula for intraventricular injections was inserted into right lateral ventricle. The animals were deprived of paradoxical sleep by the method of Jouvet[4] et al. for 3 days and nights. After 3 days and nights they were put into a soundproof chamber and their EEG were recorded, by Alvar VIII channel electroencephalograph, for 6 h. The cats were then allowed to rest for 10 days and the deprivation procedure of the same duration was repeated. The animals were again put into the soundproof chamber and after the first episode of paradoxical sleep appeared, adrenaline hydrochloride was administered intraventricularly. The % of wakefulness, slow sleep and paradoxical sleep was calculated from EEG-records.

The results obtained indicate an adrenaline action in 2 directions: suppression of paradoxical sleep, and promotion of wakefulness. The only component in sleep-wakefulness cycle which was not affected was slow wave sleep. This is shown in the Figure. In control experiments the quantity of paradoxical sleep ($23.0 \pm 4.9\%$) was, after intraventricular injection of adrenaline (0.2–2.0 mg), reduced ($8.0 \pm 4.4\%$). The EEG-pattern of paradoxical sleep after intraventricular administration of adrenaline remained unaltered. The episodes of paradoxical sleep usually occurred in the middle and in the second half of the recording time. The duration of the episodes of the paradoxical sleep was similar to those in control experiments. The increase of wakefulness ($58.0 \pm 11.8\%$) after intraventricular administration of adrenaline compared

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