Diurnal fluctuation of sensitivity to noradrenaline in the rat and thyroid adrenal interaction

V. M. Petrović and Katica Maksimović

Institute of Physiology and Biochemistry, Faculty of Science and Department of Endocrinology, Institute for Biological Research, Belgrade (Yugoslavia), 23 October 1978

Summary. Diurnal fluctuation of the sensitivity to noradrenaline, which disappeared after thyroidectomy, was restored after novotyrol treatment. Dexamethasone treatment did not result in the restoration of the diurnal fluctuation of noradrenaline calorigenic action in adrenalectomized animals.

It has been shown that heat production in rats adapted to 19-22°C and treated with the same amount of noradrenaline (1.6 mg/kg b.wt) was significantly higher in evening than in morning experiments, indicating the existence of a diurnal fluctuation of the sensitivity to this hormone. It was also found that a consequence of thyroidectomy was a complete disappearance of differences in the sensitivity between the morning and the evening experiments[1]. In order to obtain more precise information on the mechanism involved in the diurnal fluctuation of noradrenaline calorigenic action the present experiment was undertaken.

Materials and methods. Observations were made on 10 groups of albino male rats of Wistar strain, weighing 180-210 g, each consisting of 10-12 animals. Adaptation and treatment of animals as well as the oxygen consumption measurement were performed as described previously[1]. Thyroidectomy and adrenalectomy were performed under ether anesthesia and oxygen consumption measurements were carried out on the 9th day following the operation. 2 groups of thyroidectomized rats were treated once daily with novothyral Lek, which contain 10 µg L-3,5,3-triiodothyronine and 50 µg L-3,5,3,5 tetraiodothyronine. 2 other groups of adrenalectomized animals were treated with dexamethasone Lek, 1 mg/animal once daily during the period of 5 days. The control groups were treated with 1 ml of 0.9% NaCl solution only. The level of significance was determined using the Student t-test.

Results and discussion. Heat production under the influence of the same amount of noradrenaline, expressed in calories per $m^2/24$ h (figure 1), was significantly higher in thyroidectomized and novothyral-treated animals than in thyroidectomized ones both in morning and evening experiments ($p < 0.01$). Besides, in the period when the maximum effect was registered in the evening experiments (25, 35 and 45 min following the injection of noradrenaline) the difference between morning and evening experiments in novothyral-treated groups was statistically significant ($p < 0.01$, $p < 0.01$ and $p < 0.05$ respectively). These results suggest that the diurnal fluctuation of the sensitivity to the injected noradrenaline depends, at least in part, on the presence of thyroxine and triiodothyronine in the tissues. This is in agreement with some previous findings concerning circadian rhythms of general metabolism in normal control and thyroidectomized rats[2].

As the circadian rhythm of adrenocortical activity was found[3-5] we suspected that the adrenals might be also involved in the control of diurnal fluctuation of the sensitivity to noradrenaline supplied. To investigate this possibility we examined the effect of noradrenaline in adrenalectomized rats before and after treatment with dexamethasone. As shown in figure 2, adrenalectomy had as a consequence a complete disappearance of diurnal fluctuation of noradrenaline calorigenic action. However the injected noradrenaline still produced a significant increase in the heat production in both morning and evening experiments ($p < 0.01$). When treated with dexamethasone (figure 3) adrenalectomized rats showed a significant increase in the heat production under the influence of noradrenaline, in both evening and morning experiments ($p < 0.01$). However, the differences between evening and morning groups were not significant ($p > 0.05$). It is to be pointed out that the potentiated effect of dexamethasone

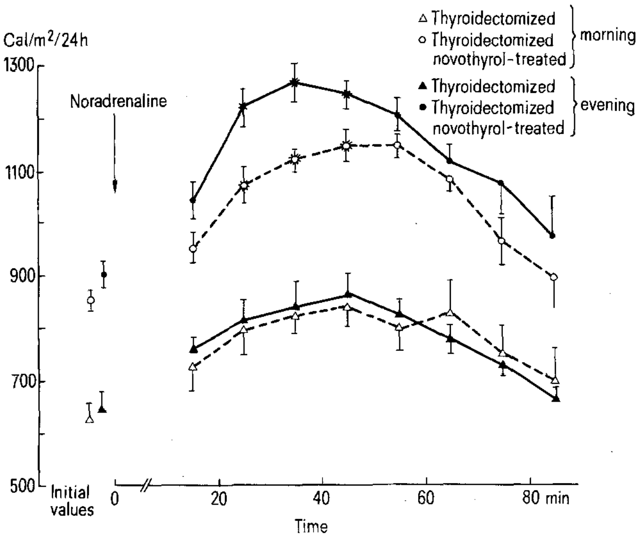

Fig. 1. The effect of noradrenaline (1.6 mg/kg) on the heat production in the rat adapted to 19-22°C and measured at 30°C. Thyroidectomized: measurement made in the morning (07.00 h, △—△) and in the evening (20.00 h, ▲—▲). Thyroidectomized and treated with novothyrol: measurement made in the morning (○—○) and in the evening (●—●). Mean ± SEM of 10-12 animals. The asterisks indicate values where the differences between the morning and evening measurements were significant.

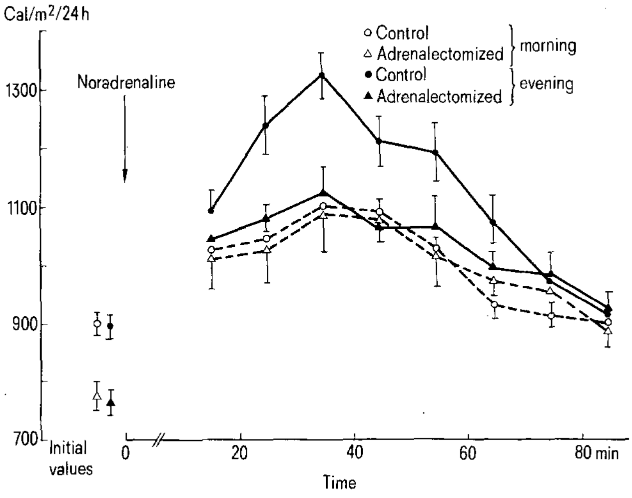

Fig. 2. The effect of adrenalectomy on the heat production under the influence of noradrenaline. In the morning experiment: ○—○, control; △—△, adrenalectomized. In the evening experiment: ●—●, control; ▲—▲, adrenalectomized. Mean ± SEM of 10 animals.

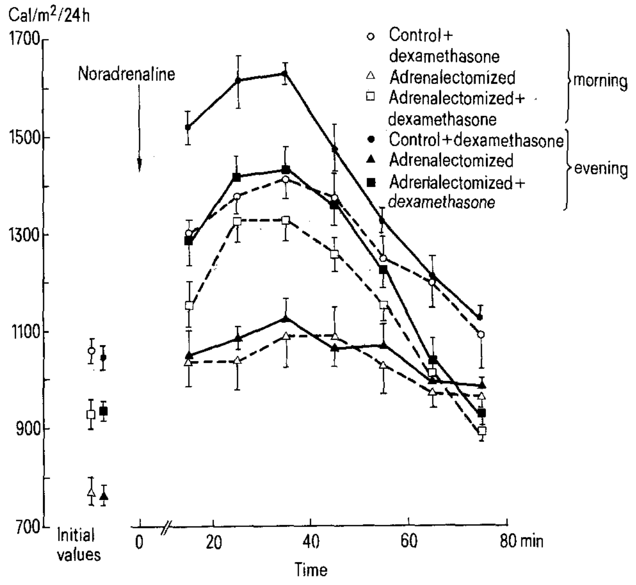

Fig. 3. The effect of dexamethasone on the heat production under the influence of noradrenaline in adrenalectomized and the control animals. Morning experiment: △—△, adrenalectomized; □—□ adrenalectomized+dexamethasone; ○—○, control+dexamethasone. Evening experiment: ▲—▲, adrenalectomized; ■—■ adrenalectomized+dexamethasone; ●—● control+dexamethasone. Mean ± SEM of 12 animals.

was registered in the control animals treated with noradrenaline. In these animals the diurnal fluctuations of the sensitivity to this hormone were markedly expressed, the differences between morning and evening experiments being significant ($p < 0.01$).

The evidence that in adrenalectomized animals the diurnal fluctuation of the sensitivity to injected noradrenaline was not restored after the treatment with dexamethasone suggests that this phenomenon is not linked to the presence of glycocorticoids only, but probably to the circadian fluctuation of the adrenocortical activity.

In conclusion, from the results reported here, taken together with our previous findings[1], it may be assumed that the diurnal fluctuation of the sensitivity to injected noradrenaline is the consequence of thyroid-adrenal interaction. The phenomenon is probably linked to the circadian fluctuation of adrenocortical activity, but as shown, the thyroid hormones are markedly involved in its expression.

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A wide spectrum of resistance to pyrethroid insecticides in *Musca domestica*

D.H. DeVries and G.P. Georghiou

Division of Toxicology and Physiology, Department of Entomology, University of California, Riverside (California 92521, USA), 18 April 1979

Summary. Selection of a strain of house flies with the pyrethroid bioresmethrin has resulted in a wide range of cross resistance to 15 other pyrethroid insecticides.

In the past 30 years, over 364 species of arthropods have developed resistance to 1 or more insecticides[1]. One of the principal approaches for countering resistance involves the synthesis of new insecticides that are effective on these resistant strains. At the same time, society requires that new insecticides be safe to mammals and that they not persist in the environment. The natural pyrethrins, extracts from the flower of *Chrysanthemum cinerariaefolium,* are safe to mammals, but they are too unstable for field use. Elliott has succeeded in synthesizing many analogs of the compounds, which are referred to as synthetic pyrethroids[2-5]. The mammalian/insect selectivity ratio for pyrethroids was reported to be 4500 as compared to 16, 33, and 91 for carbamates, organophosphates, and organochlorines, respectively[6], and as a class, these compounds are relatively unstable and do not accumulate in the environment[6]. The requirements that they should not be affected by existing resistance and that they should not be prone to induce resistance to themselves are somewhat more difficult to satisfy, but encouraging results were given by Keiding when he reported that a mixture of natural pyrethrins plus piperonyl butoxide (p.b.) had been used for 20 years to control house flies on Danish farms without any resistance developing[7]. In the last 3 years, however, a few cases of resistance to both natural pyrethrins and synthetic pyrethroids have been reported with the following levels of resistance or cross resistance in field-selected populations: *Musca domestica,* 105× toward bioresmethrin[7]; *Aedes aegypti,* 30× toward permethrin[8]; *Boophilus microplus,* 10× toward cypermethrin[9]; *Spodoptera littoralis,* 4× toward permethrin; and *S. exigua,* 2000× toward permethrin (J.S. Holden, personal communication). In addition, laboratory selections have resulted in 75× resistance to natural pyrethrins plus p.b. in *Blattella germanica*[10], > 4000× resistance to trans-permethrin in *Culex pipiens quinquefasciatus*[11], and 250× resistance to natural pyrethrins and 100× resistance to resmethrin in *Musca domestica*[12].

Resistance to pyrethroids could be due to detoxification of individual insecticides at sites susceptible to enzymatic attack. Such is often the case with carbamates and organophosphates. Another possibility is that resistance to all members of the pyrethroid group could be developed by the reduction of sensitivity at the active site, as is presumed to be the case with resistance to cyclodienes[13]. The type of resistance that can be induced by a particular pyrethroid is thus a most important question: if it is of the metabolic type, it could be circumvented by appropriate alteration of molecular structure, but if it is of the insensitivity type, solutions become untenable since resistance may extend to all other pyrethroids. Here we are reporting that, in our pyrethroid-resistant strain of *Musca domestica* (strain SBC), resistance appears to be of the latter type. This suggestion is