INCREASE IN THE RATE OF NORADRENALIN TURNOVER IN THE HYPOTHALAMUS AFTER ADRENAL DEMEDULLATION (POTENTIATION OF THE EFFECT OF DISULFIRAM IN EXHAUSTING THE NORADRENALIN RESERVES)

A. M. Baru, M. S. Rasin, and I. Ya. Braude

UDC 612.826.4.018-06:612.45.014.46:615.246.9:547.496.2

Administration of disulfiram, a dopamine-β-oxidase inhibitor, after adrenal demedullation is accompanied by a sharper decrease in the noradrenalin content in the hypothalamus than in animals with intact adrenals. This operation had no such action on the change in noradrenalin content in the heart and cerebral hemispheres resulting from administration of disulfiram.

The work of Baru [1, 2] has shown that exhaustion of noradrenalin (NA) reserves of the central nervous system is accompanied by activation of the adrenalmedulla, with an increase not only in secretion, but also in synthesis of the hormone. These interrelationships are considered to reflect reciprocity between the noradrenergic structures in the central nervous system and peripheral adrenomedullary structures and they may play an important role in the function of the sympathico-adrenal system in stress and in pathological states.

As the next stage in the study of this problem it was decided that, in addition to information on the increase in adrenomedullary activity associated with exhaustion of the central noradrenergic structures, information must also be obtained on the state of these noradrenergic structures after inactivation of the adrenalmedulla.

Accordingly, in the investigation described below, the effect of adrenal demedullation on the NA concentration in the hypothalamus, the cerebral hemispheres, and the heart of albino rats was studied during inhibition of NA synthesis by disulfiram, i.e., in a type of experiment designed to study the rate of turnover of the mediator as the most adequate biochemical index of activity of adrenergic neurons [4].

EXPERIMENTAL METHOD

Experiments were carried out on 25 male albino rats weighing 190-250 g. Adrenal demedullation was performed 10-14 days before the experiment by crushing the medulla of the glands through an incision in the capsule and cortex. Animals undergoing a mock operation, with incision of the skin and fascia, mobilization of the adrenals, but no demedullation, acted as the control. Disulfiram, a dopamine-β-oxidase inhibitor, was injected intraperitoneally in 1% starch mucilage in a dose of 200 mg/kg. The rats were sacrificed 3 h later by decapitation. The concentration of catecholamines (CA) in the hypothalamus, cerebral hemispheres, and heart was determined by the trihydroxyindole method [3] with modifications described previously [2]. To verify the completeness of demedullation, the excretion of CA in the urine and

Laboratory of Biochemistry, Khar'kov Research Institute of Neurology and Psychiatry and Department of Biochemistry, Khar'kov Medical Institute. (Presented by Academician V. V. Parin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 72, No. 11, pp. 23-24, November, 1971. Original article submitted March 3, 1971.

© 1972 Consultants Bureau, a division of Plenum Publishing Corporation, 227 West 17th Street, New York, N. Y. 10011. All rights reserved. This article cannot be reproduced for any purpose whatsoever without permission of the publisher. A copy of this article is available from the publisher for $15.00.

TABLE 1. Effect of Adrenal Demedullation on Changes in NA Content in the Tissues Caused by Disulfiram (M ± m)

Group of animals	NA content (in μg/g)		
	control	disulfiram	P
Hypothalamus			
Undergoing mock operation	1,47±0,12	0,74±0,10	<0,001
Undergoing adrenal demedullation	1,88±3,20	0,32±0,04	<0,001
P	>0,05	<0,01	
Cerebral hemispheres			
Undergoing mock operation	0,38±0,04	0,14±0,02	<0,001
Undergoing adrenal demedullation	0,45±0,02	0,10±0,002	<0,001
P	>0,1	>0,1	
Heart			
Undergoing mock operation	0,76±0,16	0,38±0,01	<0,05
Undergoing adrenal demedullation	0,73±0,09	0,50±0,05	0,05
P	>0,5	<0,05	

Note: Each group consisted of 5-6 animals.

the CA content in the adrenal tissue remaining after the operation were also determined.

EXPERIMENTAL RESULTS

On the 11th-12th day after adrenal demedullation the adrenalin excretion was much lower (0.015 ± 0.01 μg) than in the control animals (0.17 ± 0.002 μg), while NA excretion was doubled (normal 0.35 ± 0.02 μg, experiment 0.70 ± 0.17 μg). These results, together with the extremely low CA content in the residual adrenal tissue (not more than $^1/_{40}$ of normal) indicated that the operation had been effective. The NA content in the hypothalamus, cerebral hemispheres, and heart was not significantly changed in the demedullated animals. Injection of disulfiram caused a marked decrease in the NA content in all tissues investigated from both the control and the experimental animals. However, whereas in the rats subjected to the mock operation disulfiram caused an approximately equal decrease in the NA content in the heart, cerebral hemispheres, and hypothalamus, in the animals subjected to adrenal demedullation the greatest decrease in NA content was observed in the hypothalamus (Table 1). The NA content in the heart actually increased slightly.

Since, when NA synthesis is blocked, the degree of exhaustion of its reserves in the tissues reflects the intensity of utilization of the mediator, these results indicate that after adrenal demedullation the consumption of NA in the hypothalamus is sharply increased. However, demedullation itself does not cause any decrease in the NA reserves in the hypothalamus but, on the contrary, there is actually a tendency for its concentration to increase. The possible reason may be that besides an increase in consumption, the biosynthesis of NA is also increased, i.e., there is a quickening of its turnover, indicating a marked increase in activity of the central noradrenergic neurons.

An earlier investigation by the same method (blocking NA synthesis) showed that exhaustion of the NA content in the brain is accompanied by a more rapid turnover of adrenalin in the adrenals [2]. The results described above largely confirm this hypothesis of the existence of reciprocal relationships in the system consisting of the central noradrenergic structures and the adrenal medulla, laying particular emphasis on its hypothalamic mechanisms.

LITERATURE CITED

1. A. M. Baru, in: Proceedings of the Fourth All-Union Conference on Biochemistry of the Nervous System [in Russian], Tartu (1966), p. 13.
2. A. M. Baru, in: The Physiology and Biochemistry of Biogenic Amines [in Russian], Moscow (1969), p. 64.
3. V. O. Osinskaya, Biokhimiya, No. 3, 537 (1957).
4. R. Würtman et al., Anesthesiology, 20, 714 (1968).