Importance of Pineal Gland Interactions with the Sympathoadrenal System for the Depressant Action of Reserpine

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Reserpine lowered norepinephrine and dopamine levels in the hypothalamus of rats, particularly after pinealectomy. On the other hand, its effects on catecholamine levels in the adrenals of pinealectomized rats were weaker than in intact animals. It is suggested that the depression produced by reserpine may be due in part to impaired interactions of the pineal gland with central and peripheral components of the sympathoadrenal system.

Key Words: *reserpine; pineal gland; sympathoadrenal system; catecholamines*

One of the central properties of reserpine is its ability to produce depression. Although the origin of this effect has traditionally been ascribed to impaired activity of reticular and limbic structures in the brain, there is evidence that its depressant action may also be due to defective operation of the sympathoadrenal system (SAS), whose strained functioning is an inevitable accompaniment of affective disorders [5,6]. One cause of these disorders may be malfunction of the pineal gland (which supplies endocrine secretions for periodic processes), in particular because of upheavals in hypothalamic-pituitary-adrenal mechanisms [1]. In view of this, we decided to examine how the pineal gland might contribute to the ability of reserpine to influence catecholamine metabolism at the central (hypothalamus) and peripheral (adrenals) levels of the SAS.

MATERIALS AND METHODS

The study was conducted on random-bred male rats (body weight 100-130 g) during spring and summer months. The animals were divided into nine groups, as shown in Table 1. Physiological saline was given in repeated injections over a prolonged period, while melatonin was injected at 0.1 mg/kg once daily for 10 days. Reserpine was injected in a dose of 2 mg/kg 24 h before the assays for catecholamines (in the melatonin-treated group, it was given after the last melatonin injection). All three substances were administered by the intraperitoneal route. Pinealectomy was performed under Nembutal anesthesia using a modified procedure developed by K. B. Ovanesov in our laboratory. The sham operation involved trephining of the skull and raising a bone flap without extirpating the pineal gland. Norepinephrine (NE) and dopamine (DA) concentrations in the hypothalamus and adrenals were measured fluorimetrically [4] after their removal from rats decapitated under ether anesthesia.

All rats were kept in the vivarium under natural illumination and had free access to food and water, care being taken to standardize, as far as possible, the temperature conditions and dietary regimen in the different groups.

The results were subjected to statistical treatment using Student's t test to estimate the significance of intergroup differences.

RESULTS

Hypothalamus. Hypothalamic levels of both catecholamines in the intact rats were similar to those re-

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TABLE 1. Effect of Reserpine on Catecholamine Levels (ng/mg Tissue) in the Hypothalamus and Adrenals of Intact and Pinealectomized Rats (*M±m*)

Treatment	Hypothalamus		Adrenals	
	NE	DA	NE	DA
None (intact rats)	3.37±0.27	3.28±0.21	125±9.46	6.3±0.54
Saline	12.05±0.5***	12.02±1.5**	41.5±2.7***	2.41±0.49***
Reserpine	2.2±0.37***	2.8±0.61**	2.06±0.81***	3.92±0.61*
Pinealectomy	5.32±3.08	5.65±0.83**	47.7±4.11***	2.05±0.44***
Sham operation	5.58±1.43*	5.97±0.69****	94.58±8.74****	6.23±1.44
Pinealectomy+reserpine	0.83±0.26*****°°°	1.41±0.47*****	57.4±24.76*°°°	3.59±0.86*
Sham operation+reserpine	0.77±0.17******°	0.96±0.29*******	110±14.28***°°°	4.12±0.42**
Melatonin	6.6±1.5***	5.5±1.39*	27.26±2.7*****	7.7±0.84**
Melatonin+reserpine	0.45±0.08******°°	1.8±0.47****	23.98±1.7********°°	9.39±1.54**°

Note. Superscripts denote significant differences from the intact (*), saline-injected (*), and reserpine-injected (°) groups, the number of superscripts indicating the magnitude of the difference.

ported by other authors, but were significantly elevated after the repeated saline injections, apparently as a reaction to the stress caused by this intervention (Table 1). Reserpine caused drastic falls in NE and DA to 2.2 and 2.8 ng/mg tissue, respectively, i.e., to levels nearly five times lower than those recorded for the saline-treated group. If these falls are considered in relation to NE and DA levels in the intact controls, then NA appears to be more sensitive to reserpine than DA (Table 1).

The pinealectomized group had higher catecholamine levels that the three preceding groups. Reserpine administered to pinealectomized rats lowered the NE and DA levels severalfold to 0.83 and 1.4 ng/mg tissue, respectively, which indicates that noradrenergic mechanisms were involved by reserpine to a greater extent than dopaminergic. It is noteworthy that the results in the reserpine-injected pinealectomized and sham-operated groups were similar, as were the results in the two operated groups not injected with reserpine.

In the group treated with pineal melatonin, NE and DA levels were significantly lower than in the saline-treated group, but significantly higher than in the intact group. Finally, the effects from reserpine were markedly enhanced in the melatonin-treated rats, the difference in NE concentration from the group given reserpine alone being significant.

Adrenals. The results of measuring adrenomedullary NE and DA differed markedly from those obtained for these catecholamines in the hypothalamus. Thus, as can be seen in Table 1, the saline-treated rats had lower NE and DA concentrations in the adrenals than the intact animals; the reserpine-injected rats had lower NA concentrations than the saline-treated ones, but higher DA concentrations; meanwhile, pinealectomy, unlike in the hypothalamus, had effects quite different from those of the sham operation (which virtually did not alter the DA level) and considerably attenuated the effects of reserpine on NE and DA, although these effects were much more pronounced than in the sham-operated animals. Lastly, repeated melatonin injections lowered NE levels while raising DA levels in both groups treated with this hormone (Table 1).

The findings of our study leave no doubt that the pineal gland is involved in the pharmacological effects on the SAS (since both removal of this gland and melatonin modified them), although the precise mode of this involvement is not quite clear. Our results in conjunction with those reported in the literature strongly suggest that pineal factors act as reserpine antagonists, at least vis-a-vis hypothalamic structures, and thus impose a limit on its capacity to produce depression. This hypothesis is supported by the following evidence.

On the one hand, both reserpine treatment and affective disorders are associated with lowered concentrations of cerebral catecholamines in human patients [5,6] and, on the other, biologically active pineal compounds mitigate depressive symptoms [1]. Limitation of the activity of pineal factors may augment the depressant effects of reserpine, for this compound inhibits pineal function, which results in decreased melatonin secretion [8], and melatonin, in turn, is capable of inhibiting the metabolism of hypothalamic catecholamines [10]. Pinealectomy, therefore, strongly potentiates the action of reserpine, causing, as shown in the present study, still greater falls in NE and DA, whereas repeated melatonin injections produce the opposite effect. The fact that the effects of the sham operation on these hypothalamic

catecholamines were similar to those of pinealectomy lends further support to the view that any surgical intervention disturbing the flow of cerebrospinal fluid is bound to cause some pineal deficit [3,9].

The enhancement of reserpine effects by melatonin, although somewhat unexpected and, at first sight, at variance with what has been said above, may be accounted for by the sedative and hypnotic properties discovered in melatonin [2], by virtue of which the hormone should, as a pharmacological agent, boost in a nonspecific fashion the activity of depression-producing agents such as reserpine.

In contrast to the hypothalamus, no increased depletion of catecholamines by reserpine was observed in the adrenals after pinealectomy. Since pineal control over the adrenal medulla is of a constraining rather than activating type [7], the interactions between peripheral and central components of the SAS in disease need to be explored. There is some evidence that these interactions acquire a well-defined reciprocal character in depressive states, with the depletion of hypothalamic catecholamine stores being accompanied by activation of the adrenals. In the presence of pineal deficit, when the inhibitory influence of reserpine on the metabolism of cerebral neurotransmitters increases, better conditions for such reciprocity appear to be created.

On the whole, the results of this study warrant the conclusion that impairment of the relations or interactions between the pineal gland and the SAS may be an integral part of the depressant action exerted by reserpine.

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