CENTRAL ACTION OF SEROTONIN ON THE PITUITARY – ADRENAL CORTEX SYSTEM

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The action of serotonin in stimulating the function of the adrenal cortex has been demonstrated experimentally [3, 4, 9]. However, the mechanism of this effect has not been studied. In experiments in vitro, serotonin added to the incubated adrenals in a dose of 0.5-1 mg, gave a steroidogenic effect [6, 7]. The possibility that this amine acts directly on the adrenal cortex was confirmed by experiments on hypophysectomized dogs: 0.01-0.03 mg serotonin, when added to every 100 ml of blood used for perfusing the adrenals, caused a rapid and marked increase in the secretion of hydrocortisone [9]. On the other hand, the parenteral administration of serotonin to rats in a dose of 0.25-5 mg/kg was accompanied by stimulation of adrenal cortical function, which was not observed after hypophysectomy [3, 4]. It was concluded from these experiments that the pituitary participates in the mechanism of action of serotonin on adrenal cortical function.

However, experiments in which serotonin is administered parenterally cannot determine whether or not it has a central action, not only because of the poor permeability of the blood-brain barrier for this amine [5, 8], but also because this method of administration does not rule out the possibility of the primary action of serotonin on peripheral serotoninergic structures.

In the present investigation an attempt was made to discover whether serotonin may exert a central effect on the hypothalamus – pituitary–adrenal system when injected directly into the cerebral ventricles after transection of the brain stem, i.e., in experiments permitting differentiation between the central and peripheral actions of serotonin.

EXPERIMENTAL METHOD

Experiments were carried out on male guinea pigs. For subcutaneous injection the serotonin and its precursor, 5-hydroxytryptophan, were dissolved in distilled water and injected in doses of 2 and 100 mg per kg, respectively. In control experiments the corresponding volume of distilled water was injected. For administration through a cannula introduced into the lateral ventricle of the brain, the serotonin (200 μg) was dissolved in Tyrode solution warmed to body temperature and injected in a volume of 0.04 ml, after which the cannula was washed out with the same volume of Tyrode solution. The volume of the cannula did not exceed 0.02 ml. Since serotonin–creatinine sulfate was used in the experiments and the pH of the serotonin solution injected into the ventricle was 5.94, to exclude the effect of the acid medium and the creatinine solution as well as the Tyrode solution, in a special series of control experiments creatinine solution was injected in a volume equivalent to the serotonin given and with its pH adjusted to 5.94. The indicator of a change in the function of the pituitary–adrenal system was the level of 17-hydroxycorticosteroids in the peripheral blood plasma [1]. Blood for investigation was taken 1 h after injection of serotonin and 2.5 h after administration of 5-hydroxytryptophan. In the latter case this time interval can be considered adequate for a significant increase in the serotonin content in the brain [2].

EXPERIMENTAL RESULTS

The results of the preliminary investigation showed that the subcutaneous injection of serotonin causes a marked increase in the level of 17-hydroxycorticosteroids in the peripheral blood plasma (Table 1).

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Table 1. Concentration of 17-Hydroxycorticosteroids in Blood of Guinea Pigs with an Intact Brain, M ± m

Substances injected	Mode of injection	Conc. of 17-hydroxycorticosteroids (μg%)	P	No. of animals
Distilled water	Subcutan.	42,63±2,87	<0,001	20
Serotonin (200 μg)		148,69±10,28		
Distilled water	Subcutan.	50,80±4,76	<0,001	15
5-Hydroxytryptophan (100 mg per kg)		121,20±4,47		
Tyrode solution	Into the lateral ventricle	56,30±6,24	<0,002	14
Serotonin (200 μg)		127,16±19,35		

Table 2. Concentration of 17-Hydroxycorticosteroids in the Blood of Guinea Pigs with Mesencephalic Transection of the Brain, M ± m

Substances injected into lateral ventricle	Level of transection[1]	Conc. of 17-hydroxycorticosteroids (μg%)		P	No. of animals
		1 h after transection	1 h after injection (2 h after transection		
Tyrode solution	1	58,69±6,05	61,55±8,49	>0,1	6
	2	62,32±6,01	73,40±3,21	>0,1	5
	3	69,91±9,96	79,88±15,93	>0,1	6
	4	66,60±6,18	75,76±6,76	>0,1	5
Creatinine sulfate	1	54,85±5,91	51,15±4,92	>0,1	5
	3	61,72±3,57	51,98±6,64	>0,1	8
Serotonin (200 μg)	1	61,00±4,24	86,20±7,00	<0,01	17
	2	75,85±7,24	99,32±8,18	<0,05	10
	3	78,12±8,78	124,51±19,05	<0,05	8
	4	69,55±6,82	111,44±15,58	<0,05	9

[1] See figure.

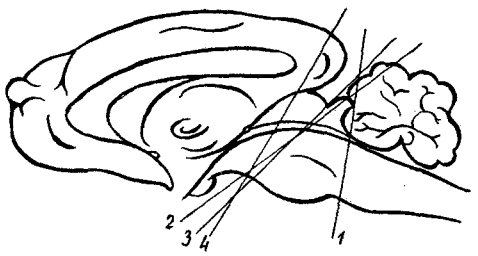

Fig. 1. Diagram showing the brain of a guinea pig. Explanation in text.

However, it could not be concluded from this fact alone that serotonin may exert a central action on the pituitary–adrenal system. At the same time, the possibility of a central action of serotonin could not be ruled out, because stimulation of adrenal cortical function was also brought about by its precursor, 5-hydroxytryptophan (Table 1), which, unlike serotonin, penetrates readily through the blood-brain barrier [2, 8].

In the next series of experiments, serotonin was injected into the lateral ventricle of the experimental animals. One hour after injection of this preparation, the concentration of 17-hydroxycorticosteroids in the blood of the guinea pigs was increased (Table 1). It was postulated on the basis of these results that serotonin may have a direct central action on the hypothalamus–pituitary–adrenal system. However, these experiments in which serotonin was injected into the ventricle of an animal with an intact brain could not completely rule out the possibility that the corresponding structures at the periphery were excited by the transmission of impulses arising in the brain, after intraventricular injection of serotonin along the efferent pathways through the spinal cord, with a subsequent secondary reaction on the pituitary–adrenal cortex system.

To differentiate between the direct central action of serotonin and its peripheral effect, in the next series of experiments serotonin was injected into animals undergoing the following types of transection of the brain stem (see figure): caudally to the inferior colliculi and to the pons; between the superior and inferior colliculi and rostrally to the pons; through the inferior colliculi and rostrally to the pons; through the superior colliculi and between the mammillary bodies and the pons.

One hour after injection of serotonin into the lateral ventricle, against the background of these types of transection of the brain, an increase in the concentration of 17-hydroxycorticosteroids was found in the peripheral blood plasma of the guinea pigs. Neither Tyrode solution nor creatinine sulfate produced such an effect (Table 2). The difference in the degree of elevation of the corticosteroid level after injection of serotonin in conjunction with the different types of transection was not statistically significant ($P > 0.05$). The results of these experiments show that serotonin, when injected into the lateral ventricle in conditions ruling out the possibility of its peripheral effect, causes stimulation of the

activity of the pituitary–adrenal system. Consequently, serotonin has a direct central action on this system.

It may be concluded that serotonin participates in the central regulatory mechanisms of the hypothalamus–pituitary–adrenal cortex system.

LITERATURE CITED

1. N. A. Yudaev and Yu. A. Pankov, Probl. Éndokrinol., No. 2, 35 (1958).
2. E. Costa, G. R. Pscheidt, W. G. van Meter, et al., J. Pharmacol. exp. Ther., 130, 81 (1960).
3. H. Miyawaki, M. Ui, and B. Kobayashi, Endocr., jap., 8, 148 (1961).
4. H. Moussatche and H. A. Pereiro, Acta physiol. lat.-amer., 7, 71 (1957).
5. J. H. Page, Physiol. Rev., 38, 277 (1958).
6. H. Rozenkrantz, Endocrinology, 64, 355 (1959).
7. H. Rozenkrantz and R. Q. Laferte, Ibid., 66, 832 (1960).
8. S. Udenfriend, H. Weissbach, and D. Bogdanski, J. Pharmacol. exp. Ther., 120, 255 (1957).
9. A. S. Verdesca, C. D. Westermann, R. S. Crampton, et al., Am. J. Physiol., 201, 1065 (1961).