MECHANISM OF ACTION OF CYPROHEPTADINE (PERITOL) ON ACTIVITY OF THE HYPOTHALAMIC—PITUITARY—ADRENAL SYSTEM

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UDC 612.826.4+612.432+612.45].014.46:615.225.2.015.23

KEY WORDS: peritol (cyproheptadine); hypothalamic—pituitary—adrenal system; serotonin.

The neurochemical and neurophysiological aspects of the regulation of endocrine functions are closely bound up with the functional metabolism of biogenic amines. The role of biogenic monoamines in the regulation of the hypothalamic—pituitary—adrenal system (HPAS) has been studied particularly intensively. The writers showed previously that peritol (cyproheptadine), which blocks serotonin receptors, has a marked inhibitory action on activity of the HPAS soon (3 or 6 h) after its administration. This is expressed as a fall in the blood levels of ACTH, corticosterone, and aldosterone in the recipients. However, during prolonged administration of peritol (10, 20, and 30 days) in the same dose (2 mg/100 g body weight) twice a day no changes were observed in the functional activity of the HPAS [8]. The writers have postulated that the absence of an inhibitory effect of peritol on activity of the HPAS during its long-term administration may perhaps be attributable to the low dosage of the drug or (if given in two separate doses) to the rapid elimination of peritol from the body and the resulting fall in its concentration both in the CNS and in peripheral tissues.

The aims of the present investigation were as follows: first, to study in relation to the HPAS dependence of the antiserotonin effect of peritol on the frequency of its administration and the dose of the drug, a matter of fundamental importance for clinical practice, where this drug is widely used (in Cushing's disease, allergic diseases of varied etiology); second, to explain certain aspects of the mechanism of action of peritol, namely: to discover whether peritol has a specific action on activity of the HPAS through the CNS or whether the point of application of the drug may be in peripheral tissues.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 180-250 g. Peritol (cyproheptadine), from "Egyt" (Hungary), was administered internally by means of a tube in the following alternative versions: 1) a dose of 2 mg/100 g twice a day for 10, 20, and 30 days; 2) a dose of 2 mg/100 g every 3 h for 10 days; 3) a dose of 2 mg/kg every 3 h for 10 days. By means of radioimmunologic and radioisotope methods the concentrations of ACTH (using kits from "Amersham Corp.," England), aldosterone (kits from CEA-IRE-Sorin, France), and corticosterone [1, 2] were determined in the animals' blood 24 h after the end of administration of peritol. The concentration of cAMP in the tissues was determined by radioisotope kits ("Amersham") after preliminary extraction of the cAMP [11]. To study the action of cyproheptadine (from "Henning," Berlin) on the concentration of corticosterone in the incubation medium and adrenal cortex, the drug was given in doses of 10^{-7} and 10^{-5} M and the tissue was subsequently processed by the method described in [3].

EXPERIMENTAL RESULTS

After administration of peritol twice a day in a dose of 2 mg/100 g for 10, 20, and 30 days no action of the drug was found on activity of HPAS: The concentrations of ACTH, corticosterone, and aldosterone in the animals' blood were within the same limits as in the control (Table 1). The duration of administration of peritol thus did not alter its effect

Kiev Research Institute of Endocrinology and Metabolism, Ministry of Health of the Ukrainian SSR. (Presented by Academician of the Academy of Medical Sciences of the USSR N. N. Gorev.) Translated from Byulleten' Eksperimental'noi Biologii i Meditsiny, Vol. 94, No. 9, pp. 71-73, September, 1982. Original article submitted March 1, 1982.

0007-4888/82/9409-1245$07.50

TABLE 1. Effect of Frequency of Administration and Dose of Peritol on Blood Levels of ACTH, Corticosterone, and Aldosterone in Rats (M ± m)

Experimental conditions	Blood hormone levels		
	ACTH, pg/ml	corticosterone, μg/100 ml	aldosterone, ng/100 ml
Intact animals	164±20	12,3±1,5	25,5±1,4
Administration of peritol in a dose of 2 mg/100g twice a day for:			
10 days	136,2±9,8	14,56±3,30	20,28±2,10
20 "	127,2±7,0	13,0±1,4	20,29±2,35
30 "	130±10	13,9±1,5	21,5±2,7
Administration of peritol every 3 h for 10 days in a dose of:			
2 mg/100 g	64,2±7,3*	7,0±1,5*	17,1±3,0*
2 mg/kg	67,8±9,2*	7,4±1,4*	18,5±2,0*

Legend. Here and in Table 2, *P < 0.05.

TABLE 2. Effect of Frequency of Administration and Dose of Peritol on cAMP Concentration in Rat Tissues (M ± m; n = 10)

Experimental conditions	cAMP concentration in undermentioned tissues, pmoles/g tissue					
	liver	pituitary	hypothalamus	brain	adrenals	thyroid gland
Intact animals	588±27	3990±190	1400±110	2090±114	1877±102	1900±150
Administration of peritol in a dose of 2 mg/100 g twice a day for:						
10 days	664±95	3622±190	1671±103	1955±95	1738±78	1716±150
20 "	531±50	3489±190	1482±150	1598±130	1791,8±109	1624±105
30 "	639±90	3224±140	1669,7±95	1830±190	1790±105	1870±230
Administration of peritol every 3 h for 10 days in a dose of:						
2 mg/100 g	320±62*	850±120*	640±137*	870±120*	425±97*	770±160*
2 mg/kg	300±87*	800±100*	670±105*	930±150*	310±80*	650±100*

as a regulator of activity of the HPAS. More frequent administration of peritol (every 3 h) in the same dose for 10 days caused a significant fall in the ACTH and steroid concentrations (Table 1). Peritol had a similar action, inhibiting the HPAS, when given in a dose 10 times smaller, but with the same frequency. It can be concluded from analysis of the results that the frequency of administration of the drug, not its dose, is of fundamental importance for peritol to exhibit its specific action on function of the HPAS.

The inhibitory action of peritol as an active blocker of serotonin receptors on functional activity of the HPAS may be presumed to be connected primarily with accumulation of peritol in a high concentration of the brain, which has a high content of serotonin [4, 7]. Serotonin is known to have a direct central action as a mediator stimulating secretion of the corresponding releasing factor in the hypothalamus — corticotrophin releasing factor (CRF). It has been shown that the pituitary–adrenal system continues to react to serotonin injected into the cerebral ventricles or locally into the hypothalamus, even after brain section when nervous connections with the periphery are interrupted. Moreover, this system reacts both to serotonin and to its precursor even after nervous isolation of the mediobasal hypothalamus [5, 6, 10, 12]. This indicates the existence of serotonin receptors connected with structures producing CRF in the hypophyseotrophic zone of the hypothalamus.

It can be concluded from the facts described above that the inhibitory action of peritol on activity of the HPAS is connected with central mechanisms, namely with blockade of serotonin receptors in the CNS [9]. Meanwhile the results of the present experiments confirm that peritol, in its influence on activity of the HPAS, has not only a central action but also a direct action on adrenal tissue. Cyproheptadine, in a dose of 10^{-7} M, has been shown to affect the corticosterone level in the adrenal cortex, whereas an increase in the

concentration of the drug to 10^{-5} M leads to a fall in the corticosterone concentration in the incubation medium and adrenal tissue from 4.0 ± 1.2 ng/100 g (control) to 1.3 ± 0.5 ng/100 g ($P < 0.01$).

Changes in the cAMP concentration in the tissues of rats receiving peritol support the view that the drug has a peripheral action on activity of the HPAS and also, evidently, of other systems and also of many metabolic and synthetic processes. The fall in the cAMP concentration in different tissues arising under the influence of peritol (which can be regarded as a peripheral action of the drug, since serotonin realizes its own effects through the adenylate cyclase system) depends to a much greater degree on the frequency of administration of the drug than on its dose and the duration of its administration. As Table 2 shows, administration of peritol in a dose of 2 mg/100 g twice a day for 10, 20, or 30 days does not affect the cAMP concentration in tissues differing in their metabolic activity and in the number of their serotonin receptors (the hypothalamus, brain, liver, and adrenals, for example). Meanwhile administration of peritol in the same dose or a dose 10 times smaller for 10 days, but given every 3 h, leads to a significant fall in the cAMP concentration in the tissues.

It can thus be concluded from these results that when peritol is described in clinical practice the frequency of its administration must be taken into account in order to maintain a sufficiently high concentration of the drug in the organs, tissues, and blood stream, so that the manifestation of its specific effect will be ensured.

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