NEUROMODULATING ACTION OF PERIPHERALLY INJECTED THYROTROPIN RELEASING HORMONE IN RAT BRAIN STRUCTURES

I. P. Misinš and V. J. Klušа

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Despite much evidence of the central action of thyrotropin releasing hormone (TRH), connected mainly with modulation of monoamine processes in the brain [1], one paradoxical phenomenon remains unexplained: the short half-life of the peptide when injected intravenously, on the one hand, and its prolonged pharmacological and clinical effect, on the other hand. It has been observed [3, 5] that intravenous injection of TRH in doses of 500 to 800 mg into subjects with endogenous depression induces a rapid antidepressant effect in them which may last from 1 h to 3 days or more. In addition it has been shown [4] that on peripheral injection of TRH, it can pass through the blood-brain barrier, to attain concentrations of 0.02-0.2% of the initial dose, depending on the method of injection. However, it is not clear, first, in which brain structures the greatest changes take place in the content of biogenic monoamines (BM) after peripheral administration of TRH, and second, how long these last.

The investigation described below was undertaken to shed light on these problems.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 200-220 g. TRH was injected intramuscularly in a volume of 0.2 ml and in doses of 1, 5, and 10 mg/kg. Rats of the control group received an injection of the same volume of physiological saline. The animals were decapitated 30 min and 1 and 3 h later, and the hypothalamus and deep brain structures including the striopallidal system and cerebral cortex were isolated. Concentrations of monoamines -- dopamine (DA) and its metabolites dihydroxyphenylacetic acid (DHPAA) and homovanillic acid (HVA), noradrenaline (NA), and serotonin (5-HT) and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) were determined spectrofluorometrically [2].

Considering the seasonal variations and instability of the BM level during the 2 years of the experiments (Table 1), the BM level in each experiment was calculated as a percentage of the corresponding control, taken as 100. The results were subjected to statistical analysis ($n = 9$) by Student's t test.

EXPERIMENTAL RESULTS

It will be clear from Table 2 that 30 min after injection of TRH in a dose of 1 mg/kg inhibition of activity was observed in the catecholaminergic system in the hypothalamus. After 1 h, with the same dose, activity in the dopaminergic system was modified, and after 3 h, catecholaminergic processes assumed a completely different character: DA metabolism was intensified along the DHPAA pathway. When doses of 5 and 10 mg/kg were used, these processes were less marked. The 5-HT concentration in hypothalamic tissue was reduced, whereas the 5-HIAA level was raised after injection of TRH in doses of 5 and 10 mg/kg. This pattern also was observed 1 and 3 h after injection of TRH in doses of 1 mg/kg.

Serotoninergic processes in the tissues of the deep brain structures, including the striopallidal system (Table 2), were in general similar in character to those in the hypothalamus, and this was particularly clear 3 h after injection of TRH. Catecholaminergic processes in this structure also showed a similar tendency: DA and NA concentrations, elevated 1 h after injection of TRH, were considerably lower after 3 h.

Distinguishing features were observed in the cerebral cortex: 30 min and 1 h after injection of TRH, DA metabolism was considerably depressed; after 1 h the NA and DA concentrations were increased (evidently due to inhibition of DA metabolism), but after 3 h the

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TABLE 1. BM Concentration in Brain Structures of Control Rats (in μg/g tissue)

BM	Hypothalamus	Striopallidal system	Cortex
NA	2,02±0,14	0,43±0,03	0,18±0,01
DA	0,47±0,04	1,49±0,10	0,22±0,02
DHPAA	0,45±0,03	0,39±0,04	0,10±0,01
MVA	0,29±0,02	0,22±0,01	0,07±0,00
5-HT	1,12±0,07	0,48±0,04	0,23±0,02
5-HIAA	0,95±0,05	0,48±0,03	0,17±0,02

TABLE 2. Effect of TRH (intramuscularly) on Concentrations of BM in Rat Brain Structures (in %)

Brain structure	Time of decapitation	Dose of TRH, mg/kg	NA	DA	DHPAA	HVA	5-HT	5-HIAA
Hypothalamus	Control (physiological saline)	—	100±7	100±9	100±6	100±6	100±7	100±5
	30 min	1	74±12*	72±5*	82±12	N. d.	115±8	103±8
		5	101±3	60±7*	95±7	98±4	66±4*	107±9
		10	101±8	67±8*	106±17	96±11	59±4*	126±7*
	1 h	1	105±8	166±17*	115±13	41±9*	69±2*	134±12*
		5	85±4*	84±11	105±11	98±6	93±3*	120±9*
		10	93±5	111±20	92±10	H. o.	110±12	118±9*
	3 h	1	73±3*	127±9*	137±7*	79±11*	59±6*	122±10*
		5	109±10	107±7	121±9*	107±5	84±7*	137±14*
		10	89±10	105±17	109±12	H. o.	74±7*	120±18
Striopallidal system	Control (physiological saline)	—	100±6	100±6	100±10	100±4	100±7	100±5
	30 min	1	104±12	100±8	104±8	135±6*	93±3	95±10
		5	107±9	94±8	226±14*	77±5*	103±4	124±10*
		10	96±11	121±10*	154±17*	85±8*	116±13	102±5
	1 h	1	126±9*	135±9*	106±6	110±4	100±4	127±7*
		5	112±3*	121±17*	108±15	78±7*	100±4	119±9*
		10	96±6	110±27	93±12	39±10*	103±9	122±7*
	3 h	1	83±3*	71±4*	83±8*	96±10	78±13*	118±5*
		5	78±9*	69±7*	119±17	84±3*	93±5	113±6*
		10	73±6*	78±3*	95±6	81±7*	77±2*	110±3*
Cortex	Control (physiological saline)	—	100±7	100±9	100±12	100±8	100±8	100±10
	30 min	1	111±15	114±16	73±9*	62±6*	94±6	101±10
		5	100±5	87±14	64±3*	38±7*	94±6	94±8
		10	104±8	92±13	84±15	112±8	91±6	130±11*
	1 h	1	115±10*	114±9	88±5	94±4	93±10	113±4
		5	114±8*	121±8*	76±7*	71±3*	92±7	125±5*
		10	108±5	124±9*	81±6*	40±7*	113±10	107±8
	3 h	1	84±4*	90±5	106±9	105±1	53±8*	118±6*
		5	87±6*	80±6*	81±5	111±10	56±2*	112±11
		10	63±1*	76±2*	100±7	60±7*	87±6	108±5

Legend. *$P \leq 0.05$ compared with control. N.d.) Not determined (HVA).

direction of the catecholaminergic processes was reversed, with normalization of levels of DA metabolites. In the serotoninergic system of the cerebral cortex TRH induced changes similar to those in the structures mentioned above, but weaker in their intensity.

The following conclusions can thus be drawn from the results on the effect of TRH on the BM system of the rat brain: 1) prolonged (3 h) changes in the catecholamine- and serotoninergic systems of the brain structures studied in responses to peripheral intramuscular injection of TRH; 2) TRH acts in opposite directions in the catecholaminergic system, but in only one direction in the serotoninergic system; 3) the strongest effect of TRH is observed in response to injection of the smallest of the doses tested, namely 1 mg/kg (if the dose was increased to 5 and 10 mg/kg, the effect could actually be reversed); 4) injection of the same dose alters the time course of activity of the system; 5) under the influence of TRH changes produced in different brain structures may be in different directions: For example, when TRH was injected in a dose of 1 mg/kg activation of the catecholaminergic system in the hypothalamus was observed after 3 h, and this was accompanied by simultaneous inhibition of its activity in the striopallidal system.

Thus despite its short half-life, TRH can induce long-term changes in the BM balance in individual brain structures; this may be one explanation of the mechanism of the prolonged action of TRH in experimental pharmacology and clinical medicine.

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AN OPIATE COMPONENT IN REALIZATION OF THE VASCULAR EFFECTS OF CLONIDINE

O. S. Medvedev

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Opiate receptors have been shown to participate in realization of the hypotensive action of clonidine in spontaneously hypertensive rats and in some patients with arterial hypertension. Analysis of naloxone-clonidine interaction in other investigations gave contradictory results. For example, naloxone inhibited the hypotensive and bradycardic effect of clonidine in normotensive rats and cats [1] and in man, whereas the results of other investigations showed that the cardiovascular effects of clonidine are realized without the participation of opiate receptors [14, 15].

In previous investigations clonidine-naloxone interaction was assessed purely on the basis of changes in blood pressure (BP) and heart rate (HR). Meanwhile the role of the cardiac and vascular components, which determine the response of BP, remained unknown.

The aim of this investigation was to study changes in the systemic and regional hemodynamics induced in anesthetized cats by clonidine and naloxone.

EXPERIMENTAL METHOD

Experiments were carried out on 18 cats of both sexes weighing from 2 to 5 kg. The animals were anesthetized with urethane and chloralose (430 ± 43 mg/kg, intramuscularly) and polyethylene catheters were introduced into the femoral artery and the femoral and external jugular veins. The cats were artificially ventilated and thoracotomy performed in the fourth left intercostal space. The transducer of a "Narcomatic RT-500" electromagnetic flow-meter was placed on the ascending part of the arch of the aorta and a catheter introduced into the left atrium. During the experiment the animals' body temperature was kept at 37 ± 0.5°C and the CO_2 concentration in the expired air at between 3.5 and 4.0 vol. %.

In the course of the experiment BP, HR, the pressure in the left atrium, the contractility (CV) of the left ventricle (dF/dt -- acceleration of the blood flow in the aorta), cardiac output, and blood flow in several organs and tissues were recorded with the use of microspheres (15 μ), labeled with ^{125}I, ^{141}Ce, ^{51}Cr, ^{85}Sr, and ^{46}Sc (from 3M Company, USA), by the method described previously [8].

All the substances for testing were dissolved in physiological saline and injected intravenously in the course of 10 min. Clonidine hydrochloride (from Boehringer, West Germany) was injected at the rate of 1 μg/kg/min, naloxone hydrochloride (from Endo Laboratories, USA) at the rate of 0.1 mg/kg/min.

Laboratory of Experimental Pharmacology, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR, Moscow.

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