MEDIATORS IN THE MECHANISM OF THE NEUROTROPIC ACTION OF THYROTROPIN RELEASING HORMONE

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Thyrotropin releasing hormone (TRH) is a tripeptide with the structure Pyr-Glu-His Pro-NH_2 and is a hypothalamic neurohormone. It possesses hypophysiotropic properties and stimulates the secretion of thyrotropin (TSH), which controls release of thyroid hormones L-triiodothyronine and thyroxine, by the anterior lobe of the pituitary. Independently of the hormonal properties of TRH, many workers have found that it stimulates nervous activity with a broad spectrum of physiological action [4-6]. Under experimental conditions TRH intensifies spontaneous motor activity, is an antagonist of barbiturates and narcotic analgesics, and induces hyperthermia. Clinical observations have shown that TRH possesses antidepressive properties: It increases interest in the environment and enhances working capacity. It has been suggested that TRH may be beneficial in patients with schizophrenia. However, the mechanism of its action is not yet clear. There are indications in the literature that a cholinergic component is present in the action of TRH, for shortening of pentobarbital sleep in mice by TRH is weakened by atropine [3]. Evidence has been obtained that TRH potentiates the excitatory effects of acetylcholine (ACh) and carbachol on single cerebral cortical neurons [5]. Kozhechkin [2], working in the writer's laboratory, showed that TRH, if applied by microiontophoresis to hypothalamic neurons in rabbits, excites neurons which are excited by ACh. The muscarinic cholinolytic atropine weakens these effects on TRH and ACh. Propranolol and the adrenolytic phentolamine do not act on this effect of TRH [2]. There is evidence that TRH has an influence on the "turnover" of noradrenalin (NA) and also, possibly, 5-hydroxytryptamine [5], and also that it is an antagonist of gamma-aminobutyric acid (GABA) [4].

It was accordingly decided to study the role of ACh, NA, and GABA in the development of the behavioral effects of TRH. To tackle this problem the method of pharmacologic analysis was used, with agonists and antagonists of the corresponding mediators. Spontaneous motor activity and the arousal effect from hexobarbital sleep in albino mice were chosen as parameters of physiological action of TRH.

EXPERIMENTAL METHOD

Spontaneous motor activity of mice was recorded by an actograph (Opto-Varimex) in 780 animals (in 10 mice sumultaneously over a period of 30 min) during the morning (10 a.m. until noon). The arousal effect was studied in 780 mice during sleep induced by hexobarbital (60 mg/kg). In all the experiments 50% of the animals acted as controls.

Atropine sulfate (5, 10, and 20 mg/kg) was used as muscarinic cholinolytic, phenylephrine (5 and 10 mg/kg), isoproterenol (0.1, 1, and 5 mg/kg), and amphetamine (5 mg/kg) as adrenomimetics, and phentolamine (5 and 10 mg/kg) and propranolol (5 and 10 mg/kg) as α- and β-adrenolytics. Muscimol (1 mg/kg) was chosen as GABA-positive drug. TRH was given in a dose of 5 mg/kg, which proved to be optimal in the chosen tests. All substances were injected intraperitoneally. Each drug was first tested separately in the above doses, after which they were given in combination with TRH in doses equal to 50% of the initial values, in accordance with the principles of study of combined action of drugs. Control animals were given an intraperitoneal injection of an equal volume of isotonic NaCl solution.

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TABLE 1. Effect of Atropine, Amphetamine, Muscimol, and TRH on Duration of Sleep Induced by Hexobarbital (60 mg/kg) in Mice (M ± m)

Experimental conditions	Dose of drug, mg/kg	Duration of sleep, min
Control	—	26±1
Atropine	10	38±3
TRH	10	20±1
Atropine + TRH	5+5	21±1
Control	—	32±2
Amphetamine	5	13±1
TRH	10	15±3
Amphetamine + TRH	2,5+5	7±1
Control	—	40±3
Muscimol	1	140±3
TRH	10	20±1
Muscimol + TRH	0,5+5	57±3

EXPERIMENTAL RESULTS

TRH (5 mg/kg) increased motor activity of the mice by 1.5-2 times and shortened the duration of hexobarbital sleep in them by 2-3 times compared with the control. Atropine (5, 10, and 20 mg/kg) reduced the motor activity of the mice and lengthened the duration of hexobarbital sleep. TRH weakened these effects considerably. Phenylephrine (5 and 10 mg/kg) and amphetamine (2 and 5 mg/kg) potentiated the motor activity of the mice and shortened the duration of their hexobarbital sleep. When TRH was combined with phenylephrine or amphetamine, an additive effect was observed. Phentolamine (5 and 10 mg/kg) and propranolol (5 and 10 mg/kg) had no effect on the motor activity of the mice or the duration of their hexobarbital sleep, but definitely weakened the stimulating action of TRH. Particularly strong inhibition of motor activity in the mice and lengthening of their hexobarbital sleep was produced by muscimol (1 mg/kg), whose action was considerably weakened by TRH.

The data in Table 1 show the effect of atropine, amphetamine, and muscimol on the action of TRH on motor activity of mice and the duration of their hexobarbital sleep. It can be postulated on the basis of these results that mediators, notably ACh, NA, and GABA, participate in the mechanism of the neurotropic action of TRH.

We may conclude by noting that TRH is a stimulator of nervous activity of a new type with a unique mechanism of action. Considering that these properties of TRH are unconnected with its hormonal action, it must be accepted that its analogs and homologs with no hormonal action are highly promising preparations for medical use.

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