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EFFECT OF THYROTROPHIN RELEASING HORMONE ON SENSOMOTOR CORTICAL NEURONS

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KEY WORDS: thyrotrophin releasing hormone (TRH); sensomotor cortex; microiontophoresis.

Thyrotrophin releasing hormone (TRH), a hypothalamic neurohormone, has a stimulating action on the CNS. If administered by peripheral or central (intraventricular) routes it induces behavioral excitation and increases locomotor activity in different animals [4, 5, 9] and also induces electroencephalographic activation [1]. TRH has been shown to have analeptic properties, for it can reduce or block the central depressant effects of barbiturates, ethanol, neuroleptics, tranquilizers, and general anesthetics [15]. These effects of TRH are not associated with any influence on the endocrine system.

It has been suggested that TRH is an endogenous analeptic, regulating the levels of wakefulness and consciousness [6]. TRH can evidently perform these functions by virtue of its effect as a chemical transmitter (mediator) or a modulator of central nervous processes.

The object of the present investigation was to make an electrophysiological study of the effect of TRH on sensomotor cortical neurons in rabbits. TRH was injected intravenously and also applied to single cortical neurons by microiontophoresis.

EXPERIMENTAL METHOD

Experiments were carried out on 14 unanesthetized rabbits weighing 3.0-4.0 kg, immobilized with diplacin* (5 mg/kg) and artificially ventilated. Action potentials (APs) of the neurons were derived extracellularly through one channel of a three-barreled glass microelectrode. The second barrel of the microelectrode was filled with an aqueous solution of TRH (0.03 M, pH 6.0). The third barrel, filled with 3 M NaCl, was used to pass the control microiontophoretic current and to compensate current artefacts. TRH for intravenous injection was dissolved in 1.5 ml 0.9 M NaCl and injected in doses of 0.1 to 7.0 mg/kg into the rabbit's auricular vein in the course of 1-1.5 min.

* 1,3-di (β-platynecinium-ethoxy) benzene hydrochloride.

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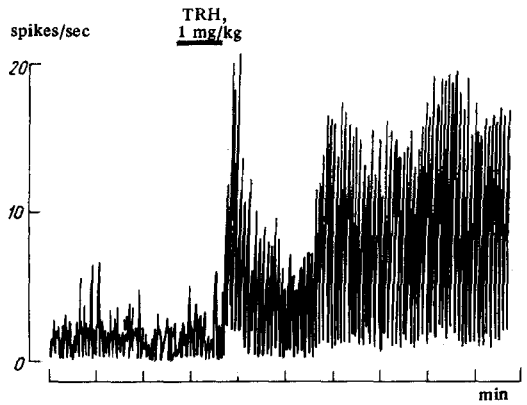

Fig. 1. Excitatory effect of intravenously injected TRH on spontaneous sensomotor cortical unit activity. Abscissa, time (in min); ordinate, discharge frequency of neuron (in spikes/sec). Horizontal line above trace indicates duration of intravenous injection of TRH in a dose of 1 mg/kg.

EXPERIMENTAL RESULTS

When injected intravenously TRH induced excitation of sensomotor cortical neurons (seven neurons in seven rabbits). TRH had a clear excitatory effect in doses as low as 0.1-0.2 mg/kg, and the effect increased with an increase in dose up to 5.0-7.0 mg/kg. The latent period of the effect was usually several tens of seconds; sometimes excitation developed extremely quickly ("to the prick of the needle"). The spontaneous discharge frequency of the cell 10-15 sec after intravenous injection of TRH in a dose of 1 mg/kg (Fig. 1) increased from 3-4 to 15-20 spikes/sec. Excitation continued as long as the neuron remained under observation (1.6 h). The excitatory effect of TRH was usually accompanied by an increase in amplitude of AP of the neurons by about 20-30%. When injection of TRH was repeated 0.5-1.5 h later in the initial dose, or even in a larger dose, tachyphylaxis was observed, in the form of considerable weakening or absence of the excitatory effect of TRH.

After microiontophoretic application of TRH to the outer surface of the membrane of the cortical neurons the discharge frequency of most of them was reduced (41 of 56). Spontaneous discharges of the remaining neurons were unchanged after application of TRH (15 of 56). With an increase in the strength of the current from 13 to 80 nA (and, consequently, by an increase in the dose of applied TRH) the depressant effect of the hormone was increased (Fig. 2). Passage of a control current, deliberately chosen to be stronger, through the microelectrode barrel filled with 3M NaCl did not change the spontaneous discharge frequency of the neuron.

The depressant effect of TRH developed usually rapidly in the course of a few seconds after the beginning of application. The initial level of spontaneous activity was restored 10-20 sec after the end of application of TRH. Incidentally, when a solution of TRH in a comparatively low concentration (0.03 M) was used, only weak currents (5-20 nA) were needed to obtain a marked effect. After both systemic and microiontophoretic administration of TRH the amplitude of the APs of the neurons increased by 20-40%.

The experimental data given above reveal opposite effects of TRH on sensomotor cortical unit activity when administered systemically (intravenously) and by direct application to the neurons by microiontophoresis.

The depressant action of microiontophoretically applied TRH on neurons of various brain structures was described previously [11]. Dependence of neuronal depression on the dose of TRH (on the strength of the microiontophoretic current), observed in the present experiments, indicates that this effect was due to interaction of TRH with specific receptors. The fact that to obtain an effect of TRH, only weak microiontophoretic currents were needed is also evidence in support of binding of the peptide with specific receptors of cortical neurons. These receptors are evidently different from those of the main chemical inhibitory transmitters of the CNS, namely glycine and GABA, for after microiontophoretic application of strychnine and bicuculline no decrease in the depressant effect of TRH was observed [11]. The increase in amplitude of APs of the neurons under the influence of TRH, mentioned above, may perhaps be due to hyperpolarization of the neuron membrane.

The results described above show that the stimulating effect cannot be explained by a direct excitatory

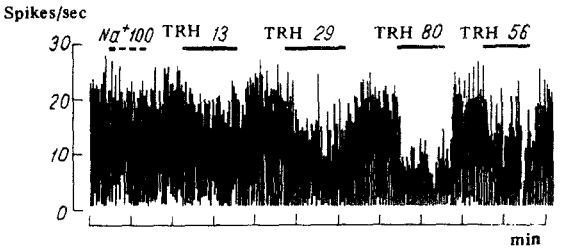

Fig. 2. Inhibitory effect of microiontophoretically applied TRH on unit activity (dependence of effect on dose of TRH). Horizontal lines above traces denote duration of microiontophoretic application of different doses of TRH, numbers above lines indicate strength of microiontophoretic current (in nA), broken line indicates passage of control current of 100 nA through microelectrode barrel filled with 3 M NaCl. Remainder of legend as to Fig. 1.

effect of TRH on one particular cortical neuron population, for no cortical neuron could be found which was excited by microiontophoretically applied TRH. The only remaining suggestion is that this activation of cortical neurons was due to intensification of the excitatory inflow into the cortex from other brain structures, whose neuronal activity was facilitated by TRH. Microiontophoretic application of TRH has been shown to have an excitatory effect on neurons of the brain-stem reticular formation [3, 7] and hypothalamus [8].

The reticular formation is known to have an excitatory effect on the neocortex. The chemical transmitter of this effect is acetylcholine [12, 13]. At the same time it has been shown [14, 16] that the excitatory effect of acetylcholine on cortical neurons is facilitated by TRH. The muscarinic cholinolytics atropine and scopolamine block the behavioral and electroencephalographic activating effects of TRH [2, 6]. Hence it can be postulated that the excitatory effect of TRH, when administered systemically, is due to strengthening of the activating influences of deep brain structures (reticular formation, hypothalamus, etc.) on the cerebral cortex. Powerful excitation of the cortex arising from deep brain structures evidently masks the direct depressant effect of TRH on cortical neurons. Only the increase in amplitude of the neuronal APs may be indirect evidence of the binding of systemically injected TRH with specific receptors of hyperpolarizing type on the neuron membrane.

In this connection it should be pointed out that biochemical experiments have revealed binding of TRH mainly with receptors of the cerebral cortex, midbrain, and hypothalamus [10].

Different parts of the CNS thus contain receptors specific for TRH, of at least two types: excitatory and inhibitory. The former are evidently responsible for the principal central stimulating pharmacological effects of TRH, which are exhibited in response to its systemic injection.

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CORRECTION OF PSYCHODEPRESSANT EFFECTS OF BENZODIAZEPINE TRANQUILIZERS BY ADMINISTRATION OF PSYCHOENERGIZERS

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KEY WORDS: psychoenergizers; tranquilizers; benzodiazepines; operant activity.

The benzodiazepine tranquilizers are being increasingly used in clinical practice, including for the correction of neurotic states in clinically healthy subjects. Besides their marked antineurotic action, these substances may induce psychodepressant effects, which restrict their use in the working population. Together with the search for new benzodiazepines free from the undesirable effects mentioned above, in order to widen the indications for the use of existing preparations the search can be made for substances correcting this psychodepressant action. Such a corrector must satisfy the following demands: it must abolish the psychodepressant action of the tranquilizer but must not introduce modifications into the optimal character of the therapeutic activity of the tranquilizer as established previously, and it must likewise not reduce the tranquilizing effect of the correcting agent. Correcting properties of substances belonging to the amphetamine group have been demonstrated previously in relation to the psychodepressant effects of diazepam and phenazepam [4, 10]. However, the use of amphetamine in clinical practice is undesirable because of the possibility of development of addiction to it. The use of sydnocarb as corrector of the psychodepressant effects of phenazepam is highly effective under experimental conditions [2]. However, indications for the use of this combination are even more restricted than those for phenazepam alone [1]. The writers previously demonstrated the high and optimal corrective activity of substances with primarily dopaminomimetic properties [4, 6].

It was accordingly decided to investigate the corrective properties of other classes of compounds which possess elements of a psychostimulant action. Particular interest was shown in the effect of so-called psychoenergizers on the central effects of benzodiazepine tranquilizers. The effect of acephen, mefexamide, euclidane (nicametate citrate), and actebral (cyprodenate) on the psychodepressant action of diazepam and phenazepam was studied in the investigation described below.

EXPERIMENTAL METHOD

Experiments were carried out on 54 noninbred male albino rats. The active avoidance method [11] was used to assess the psychotropic effects of the various substances. Experiments were carried out in a situation and by a program which were fully described previously [7]. The characteristics of the experimental program were: the time of discontinuing the painful electrical stimulation after a single pressure on the pedal was 20 sec, the following frequency of the stimuli was once every 5 sec, and their duration 1 sec. An alternating current with frequency of 50 Hz and with the current strength stabilized at 1 mA irrespective of the resistance of the object was used for stimulation. In the course of the experiment the character of operant activity was recorded graphically and the number of shocks avoided was counted automatically. During subsequent processing of the data histograms of distribution of intervals between pressures on the pedal of different duration were constructed for each animal. Twenty classes were distinguished, each 1 sec in duration. The histograms were used to describe the optimality of the character of operant activity, and the number of avoided electric shocks reflected its resultativeness [9]. Stress-protective activity of the combination of drugs tested was assessed by the same method. Operant activity was tested after the animals had been securely immobilized for 1 h. Experiments were carried out on previously trained animals which missed not more than 60 shocks during an experi-

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