EFFECT OF CHOLECYSTOKININ ON DOPAMINE METABOLISM IN THE RAT BRAIN

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KEY WORDS: cholecystokinin; dopamine metabolism; food behavior.

In several regions of the brain, the octapeptide cholecystokinin (CCK), which can specifically induce food behavior [1], coexists with dopamine (DA) in the same neurons [2]. Accordingly, the problem of the action of CCK on neuronal DA activity is one of great interest.

In this investigation, the character of the effect of CCK on the DA system was assessed in relation to parameters of DA metabolism.

EXPERIMENTAL METHOD

Male Wistar rats weighing 200-250 g were used. The sulfated octapeptide CCK (Institute of Medical Chemistry, Szeged, Hungary) was diluted in 0.9% NaCl solution and injected intraperitoneally into the animals in doses of 5, 15, and 30 μg/kg. The rats were decapitated 30 min later and the concentrations of noradrenalin (NA), DA, homovanillic acid (HVA), and dihydroxyphenylacetic acid (DHPAA) in different parts of the brain were determined by the method in [3]. Fluorescence was measured on the Hitachi MPF-2a spectrofluorometer. Student's t test was used for statistical analysis of the results.

EXPERIMENTAL RESULTS

CCK, injected intraperitoneally, significantly increased the concentrations of DA metabolites (HVA and DHPAA) in the nucleus accumbens and amygdala, but did not affect their concentrations in the midbrain, hypothalamus, and striatum (Table 1). The NA and DA concentrations were unchanged in these regions. An increase in the concentration of metabolic products of DA under the influence of CCK in these brain regions suggests that this neuropeptide increases release of the neurotransmitter DA in the mesolimbic DA system.

Doses of CCK acting on DA metabolism were close to those causing its specific behavioral effect, namely, inhibition of taking food. The effect of CCK on animal behavior may thus be partly due to its action on the function of the mesolimbic DA system, where the two substances coexist in the same neurons.

TABLE 1. Effect of CCK (15 μg/kg) on Content of NA, DA, DHPAA, and HVA (in ng/g) in Rat Brain

Substance studied	Substances injected	Midbrain	Hypothalamus	Amygdala	Nucleus accumbens	Striatum
NA	Physiological saline	563,6±72,0	1367,5±129,5	447,1±20,9	542,0±26,4	376,5±26,9
	CCK	599,9±21,0	1333,8±119,1	461,7±16,5	531,9±31,1	355,3±26,9
DA	Physiological saline	570,7±42,9	546,4±76,1	315,5±18,9	1244,5±88,4	10954,7±711,3
	CCK	577,7±59,5	632,2±120,3	321,7±20,5	1263,9±108,2	11005,3±737,1
DHPAA	Physiological saline	177,4±21,3	273,7±48,1	309,6±20,5	754,7±56,2	1373,1±87,2
	CCK	255,7±52,1	209,7±52,6	850,2±103,9*	1709,9±182,9*	1373,9±96,2
HVA	Physiological saline	192,1±29,8	180,2±13,1	428,9±20,1	626,5±30,5	884,8±51,2
	CCK	205,9±21,5	197,8±20,9	647,6±50,9*	1138,7±86,7*	871,0±42,4

*$P < 0.001$ compared with control.

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EFFECT OF DIAZEPAM ON EVOKED UNITARY RESPONSES OF HIPPOCAMPAL SLICES

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Compounds of the benzodiazepine series (BDZ) have become widely used in recent years in medical practice as tranquilizers and anticonvulsants [1]. Despite many investigations, the mechanism of the effect of BDZ has not yet been completely studied [4]. With the discovery of brain formations sensitive to BDZ, notably the limbic system [9], the necessity has arisen for a study of the effects of BDZ at the synaptic level, i.e., of the possible effect of BDZ on neurotransmitter or other cellular and subcellular systems through which BDZ may exert their influence on the neuron.

The object of the present investigation was to examine the effect of diazepam (a member of the BDZ) on evoked potentials (EP) arising in hippocampal area CA_1 in response to stimulation of Schaffer's collaterals (SC).

EXPERIMENTAL METHOD

Experiments were carried out on surviving hippocampal slices from C57BL/6 mice by the method described previously [2, 10]. The animals were decapitated, the bones of the upper part of the skull removed, and a transverse slice of the hippocampus was excised and placed in an experimental chamber through which balanced Hanks' salt solution at 25°C flowed continuously; the solution was saturated with a gas mixture consisting of 95% O_2 and 5% CO_2. Bipolar glass stimulating electrodes filled with Hanks' solution were introduced into the radial layer, where SC running from neurons of area CA_3 to neurons of area CA_1 are located, and the recording glass microelectrode, also filled with Hanks' solution, was inserted into area CA_1 (Fig. 1A).

Recording of the response began 1 h after preparation of the slice, when its electrophysiological parameters were stabilized. Pulses 0.2 msec in duration with a frequency of 0.1 Hz and a voltage of 30-60 V were used for electrical stimulation. The conditions of stimulation were chosen so as to evoke a population spike (PS), which is the synchronous discharge of pyramidal neurons in area CA_1 [5], and whose amplitude reflects the reactivity of this hippocampal synaptic system.

The diazepam used was synthesized by the method described previously [8]. The resulting preparation was purified by liquid chromatography on Sephadex LH-20 (from "Pharmacia," Sweden) in 70% methanol. The chemical structure was confirmed mass-spectrometrically. After preparation of a solution of diazepam in phosphate buffer, saturated at 4°C, its concentration (3.96×10^{-5} M) was determined from the coefficient of molar extinction (ε = 31,800 at a wavelength of 233 nm) measured in preliminary experiments, and from this solution a standard Hanks' solution was prepared. A proprietary preparation of diazepam (Seduxen, Hungary) also was used in the form of a solution in ampuls for injection. The results were recorded on photographic film and on disks of the PDP-8 computer, and were processed manually and by a program composed by A. G. Gusev [3].

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