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EFFECT OF GAMMA-AMINOBUTYRIC AND GAMMA-HYDROXYBUTYRIC ACIDS ON RATE OF ^{14}C-LEUCINE INCORPORATION INTO PROTEINS OF THE GASTRIC MUCOSA AND HYPOTHALAMUS

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KEY WORDS: experimental ulcer; gamma-aminobutyric acid; gamma-hydroxybutyric acid; ^{14}C-leucine.

Gamma-aminobutyric acid (GABA), the mediator of inhibition in the central nervous system [1, 6-8] of vertebrates, performs at the same time general metabolic functions in the brain and effector organs [2, 3]. GABA has the property of increasing the blood supply to the brain [4], of protecting animals against experimental gastric ulcers [5], and of exerting a stronger anti-ulcerative effect in conjunction with gamma-hydroxybutyric acid (GHBA).

The choice of the experimental approach described below was dictated by the whole course of our previous work. Renewal of proteins in the hypothalamus and gastric mucosa, in animals with experimental ulcers under the influence of GABA and GHBA was investigated with the aid of ^{14}C-leucine and the distribution of radioactive GABA in the body was studied.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred rats. A gastric ulcer was induced in the animals by crushing the pyloroduodenal region for 10 min.

From the time of infliction of mechanical trauma, the experimental animals of one group began to receive GABA in a dose of 40 mg/kg three times a day, whereas rats of another group received GHBA in a dose of 100 mg/kg by the same scheme. On the second day all the experimental and control animals were given an injection of 50 μCi of ^{14}C-leucine (specific radioactivity 240 mCi/mmole). The animals were decapitated 3 h later and the peritoneal cavity opened. Weighed samples of tissues were taken for examination from the gastric mucosa and the hypothalamus. Protein obtained from the tissues was solubilized in 0.5 ml of Protosol (from New England Nuclear Corp., USA). After complete solubilization of the residue, radioactivity was measured quantitatively on an SL-30 scintillation spectrometer (from Intertechnique, France), in accordance with a program designed to count ^{14}C against an external standard. The counting efficiency of ^{14}C was 95%. In a special series of experiments, in order to study the distribution of radioactive GABA in the organs of the rats, ^{14}C-GABA was injected intraperitoneally in a dose of 50 μCi into intact and control animals, and 3 h later its concentration was determined on the SL-30 scintillation spectrometer in tissue homogenates from the gastric mucosa, liver, and hypothalamus. The results were expressed in cpm/g wet weight of tissue.

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TABLE 1. Degree of Incorporation of ^{14}C-Leucine (in cpm/g protein of fresh tissue) into Rat Tissue Proteins (M ± m)

Experimental conditions	Gastric mucosa ($\cdot 10^6$)	Hypothalamus ($\cdot 10^5$)
Control	1,707±0,135	1,217±0,175
Animals with gastric ulcer	1,407±0,216	2,023±0,282
Animals with gastric ulcer receiving GABA	2,555±0,29	3,233±0,234
Animals with gastric ulcer receiving GHBA	2,248±0,354	2,311±0,166

TABLE 2. Distribution of ^{14}C-GABA (in cpm/g protein of fresh tissue) in Various Rat Tissues (M ± m)

Experimental conditions	Hypothalamus	Gastric mucosa	Liver
Control	$7{,}37 \cdot 10^4 \pm 6{,}26 \cdot 10^3$	$3{,}48 \cdot 10^5 \pm 8{,}48 \cdot 10^3$	$6{,}9 \cdot 10^5 \pm 5{,}08 \cdot 10^4$
Animals with gastric ulcer	$10{,}01 \cdot 10^4 \pm 8{,}78 \cdot 10^3$	$3{,}98 \cdot 10^5 \pm 3{,}45 \cdot 10^4$	$5{,}56 \cdot 10^5 \pm 9{,}04 \cdot 10^3$

EXPERIMENTAL RESULTS

Radioactive leucine injected into the intact animals was incorporated in the course of 3 h into proteins of the gastric mucosa and hypothalamus (Table 1). In the control animals, 24 h after trauma to the pyloroduodenal region, the formation of multiple ulcers, erosions, and hemorrhages was accompanied by slowing of incorporation of ^{14}C-leucine into a protein of the gastric mucosa by 12%, whereas incorporation of radioactivity into proteins of the hypothalamus increased by 34%.

GABA, which protected the animals against experimental gastric ulcers, increased the rate of incorporation of ^{14}C-leucine into protein of the gastric mucosa by 82%, reflecting increased intensity of trophic processes. A further increase in the incorporation of radioactive leucine into proteins of the hypothalamus thereupon takes place, while the development of experimental gastric ulcers is prevented under the influence of GABA.

The results of the investigation with GHBA showed that the rate of incorporation of ^{14}C-leucine into proteins of the gastric mucosa increased by 60%, but into proteins of the hypothalamus by only 14%. A distinct difference was thus revealed in the effects of GABA and GHBA, as reflected in the changes in the level of protein renewal in the mucous membrane and, in particular, in the hypothalamus.

^{14}C-GABA, injected interaperitoneally, was distributed irregularly in the internal organs: Its highest concentration was found in the liver and stomach, and there was appreciably less in the hypothalamus (Table 2). In experimental gastric ulcers, its concentration in the hypothalamus and gastric mucosa was increased by 36.3 and 14.6%, respectively, whereas in the liver the level of radioactive GABA fell by 19%.

It can accordingly be concluded that GABA, under conditions of delayed resynthesis of protein in the gastric mucosa affected by pathological changes, has the property of accelerating incorporation of radioactive leucine and bringing about an increase in the intensity of trophic processes. Protein renewal in the gastric mucosa was more intensive under the influence of GABA. Involvement of central nervous structures during the development of experimental gastric ulcers is demonstrated by direct experiments showing the more rapid incorporation of radioactive leucine into proteins of the hypothalamus. The results of the present experiments agree with data in the literature according to which GABA stimulates incorporation of amino acids into brain proteins *in vitro* and activates ATP synthesis in brain mitochondria [7, 8].

On the one hand, therefore, the results of these experiments are evidence of the direct participation of GABA in repair processes in the gastric mucosa in the presence of extraordinary stimulation, and on the other hand, they provide an experimental basis for the explanation of mechanisms of the central action of GABA in the protection of animals against experimental gastric ulcers. The results of the experiments to study the distribution of radioactive GABA show conclusively, moreover, that ^{14}C-GABA accumulates not only in the hypothalamus, but also in the stomach.

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CHANGES IN DEFENSIVE AND FEEDING BEHAVIOR OF RABBITS FOLLOWING REPEATED INJECTIONS OF HASHISH INTO DIFFERENT PARTS OF THE BRAIN

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KEY WORDS: hashish, hypothalamus; central grey matter of the midbrain defensive and feeding behavior.

The central mechanisms of development of addiction to hashish are still largely unexplained. Most investigations have been devoted to the discovery of brain structures concerned in the realization of a particular momentary action of hashish or of its chief active principle tetrahydrocannabinol (THC). Corresponding investigations have been made of the hallucinogenic [9], behavioral [1, 5], analgesic [13], hypothermic [15], and other effects of hashish [6, 10, 12].

Addiction to hashish is one form of pathological motivation which determines the individual's need for the narcotic, and during chronic administration it assumes the property of reinforcement; the introduction of the substance into the body abolishes the pathological motivation which has arisen. It is well known that the hypothalamic region contains centers for defensive behavior — the ventromedial nucleus [7, 8], and feeding behavior — the lateral hypothalamus [8]. Meanwhile, besides the hypothalamus, the central gray matter of the midbrain also plays an important role in the reception of nociceptive stimulation and in the realization of aggressive-defensive responses [4, 7].

It was accordingly decided in the investigation described below to study physiological responses arising during stimulation of motivation zones of the brain; the ventromedial nucleus and lateral zone of the hypothalamus and the central gray matter of the midbrain, during prolonged injection of hashish into these structures.

To differentiate the effect of hashish on the emotional-defensive response during central stimulation from its action on segmental defensive reflexes, the effect of the drug on the threshold of onset of a response to painful stimulation of the skin also was studied.

EXPERIMENTAL METHOD

Microcannulas were inserted into the parts of the brain to be studied in 12 waking rabbits weighing 3 kg by the "wandering" electrode method [2]. The design of the microcannula provided for electrical stimulation of the brain structures and injection of substances into them by means of a microinjector with an accuracy of 0.5 μl. The location of the micro-

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