The plastic character of this influence, manifested as changes in the structure of collateral responses in response to combinations of pyramidal tract stimulation and electrodermal reinforcement, may be emphasized. This last fact serves as proof of involvement of neurons of the association cortex in the mechanisms of early distinction of reinforcement, on the basis not only of extrinsic afferent information, but also of information on the structure of the pattern of the efferent spike train destined for the peripheral effectors.

Involvement of neurons of the parietal association cortex in processes of afferent synthesis and of extrapolation of the quality of reinforcement as applied to the motor act must therefore be regarded as the product of convergence of triggering afferent, collateral efferent, and also afferent reinforcing excitations, completing the elementary cycle of the motor act, and their interaction on these neurons [1, 6].

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EFFECT OF GLUTAMIC ACID AND GLUTATHIONE ON GASTRIC SECRETORY FUNCTION

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Previous investigations conducted in the writers' laboratory showed that glutamic acid (Glu), injected into the blood stream in a moderately high concentration, strongly inhibits gastric secretion through the sympathicoadrenal system [1, 3]. In the investigation described below an attempt was made to reproduce this effect by injecting Glu into the gastrointestinal tract. According to data in the literature [9, 10], Glu undergoes transamination with pyruvate in the intestinal epithelial cells with the formation of α-ketoglutaric acid and alanine. However, if its concentration is high enough, the limiting velocity of transamination can be exceeded, and some Glu passes unchanged into the blood stream. We were guided by such considerations, but could not observe any after-effects of these interrelations. The first attempts showed that Glu, used for drinking, not only does not inhibit but, on the contrary, strongly potentiates gastric secretion induced by pentagastrin. We give below the results of an investigation to study this problem.

EXPERIMENTAL METHOD

Experiments were carried out on dogs with isolated Pavlov gastric pouches (two dogs) and gastric and intestinal fistulas (two dogs). Glu (from "Reanal") was used as a solution, neutralized by the addition of NaOH to obtain monosodium glutamate (MSG). This solution (4.5% MSG)

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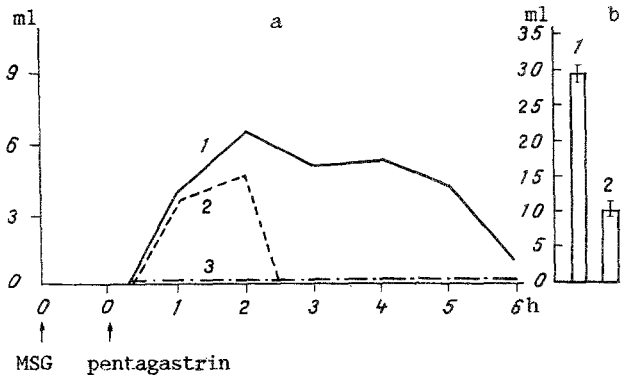

Fig. 1. Effect of drinking MSG solution on gastric secretion induced by pentagastrin. a) Course of secretion; b) volume of juice secreted during secretory period. 1) Pentagastrin + MSG; 2) pentagastrin; 3) MSG.

was given to the dogs for drinking, 16-18 h after the last meal in a volume of 70 ml, but in some experiments it was injected directly into the intestine through the fistula. Pentagastrin, in a dose inducing maximal secretion of the gastric glands (200 μg), was injected subcutaneously 1 h after drinking MSG. During infusion of glutathione into the blood stream, the volume given was equal in Glu content to half of that given to the dogs per os in the form of MSG. Gastric juice was collected every 15 min. The experimental conditions and methods of determining total acidity and free HCl, and also pepsin, were described by the writers previously [1, 2].

EXPERIMENTAL RESULTS

A solution of MSG alone, taken by the dog for drinking, did not affect the resting gastric glands and did not stimulate gastric secretion: the mucus secreted from the Pavlov pouch remained alkaline or neutral for 6 h. If drinking MSG solution was combined with subcutaneous injection of pentagastrin, it had a marked potentiating effect on gastric secretion. As Fig. 1b shows, secretion of gastric juice by a dog with an isolated Pavlov pouch, in response to pentagastrin alone, averaged 11.5 ± 2.4 ml, but when pentagastrin was combined with MSG, secretion was increased to 29.5 ± 2.4 ml. An increase in the intensity of secretion was often observed during the first 2 h of the action of pentagastrin. However, the prolongation of the secretory period from 2-2.5 h, with pentagastrin alone, to 4-5 h is particularly noteworthy (Fig. 1a). The increase in the total quantity of juice during the secretory period under the influence of MSG can be attributed mainly to prolongation of secretion. Introduction of MSG directly into the intestine through the fistula gave similar results.

The composition of the gastric juice in all these experiments was characterized by a fairly high HCl concentration and total acidity and a comparatively low pepsin content. It was not noticeably different from the composition of the gastric juice in the control (under the influence of pentagastrin alone).

In the next experiments the effect of several other amino acids was tested for comparison: alanine, valine, cysteine, and glycine. They were given to the dogs for drinking under the same conditions, and also together with pentagastrin. Alanine and valine solutions did not potentiate pentagastrin-induced gastric secretion. The other two amino acids tested caused a small increase in the secretion of juice, which was also attributable mainly to lengthening of the duration of secretion. However, both cysteine and glycine had a much weaker effect than MSG. If solutions of these amino acids were given separately (without pentagastrin), in some cases, by contrast with experiments with MSG, for a short period acid mucus was secreted from the stomach.

Besides transamination, the γ-glutamyl cycle also takes place in the intestine, and is one of the mechanisms of amino-acid transport [6, 8]. On the enterocyte membrane glutathione interacts with an amino acid entering the cell to form γ-glutamylamino acid with liberation of the Cys—Gly dipeptide. Later, the amino acid is set free and the glutamyl residue is converted through a stage of hydroxyproline back into Glu, and becomes a component of the newly formed glutathione. Thus, a complete set of the enzymes required to form glutathione from Glu

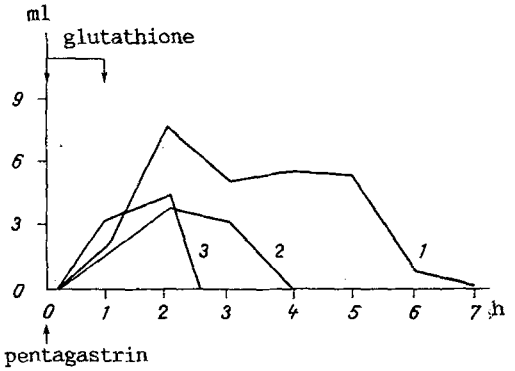

Fig. 2. Effect of intravenously injected glutathione, reduced and oxidized, on pentagastrin-induced gastric secretion. 1) Pentagastrin + reduced glutathione; 2) pentagastrin + oxidized glutathione; 3) pentagastrin.

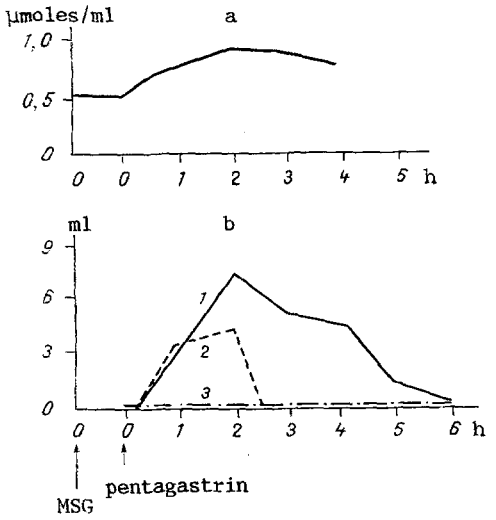

Fig. 3. Glutathione concentration in blood (a) and gastric secretion induced by pentagastrin (b) in a dog with an isolated gastric pouch, taking MSG per os. Legend as to Fig. 1.

is present in the enterocytes, and glutathione formation may probably take place easily when Glu enters the intestine. On the basis of these considerations, it might be suggested that the observed effect of Glu is connected with the formation of glutathione in the intestinal mucosa and its passage into the blood. The fact that cysteine and glycine (i.e., the component parts of glutathione), unlike the other amino acids tested, have, to some extent, a similar action also supports this hypothesis.

It was accordingly decided to study the ability of glutathione, injected into the blood stream, to influence gastric secretion. Glutathione was infused into the blood stream for 1 h in the form of a 3.6% solution in a volume of 70 ml. The experiments showed that reduced glutathione, when injected intravenously, has, in principle, the same effect on gastric secretion induced by pentagastrin as Glu administered per os (Fig. 2). Its potentiating effect also was expressed mainly as prolongation of the secretory period. The disulfide form of glutathione had a much weaker effect. Glutathione alone, without pentagastrin, did not affect gastric secretion.

Next, in conjunction with A. N. Martinchik, experiments were carried out in which glutathione was determined directly in the blood (the method was described previously [3, 11]). They showed that when MSG was taken per os there is a marked increase in the blood level of glutathione, and it coincides in time with the potentiating effect described above (Fig. 3). All these investigations suggest that the potentiating effect of Glu is due to the formation of glutathione in the intestine and its passage into the blood.

Many food proteins are known to be rich in Glu; for example, meat proteins contain about 20%, wheat proteins 34%, and casein 23% of it [7]. Glu also is present in some food products in the free form. In the countries of East Asia MSG is widely used as an additive to improve taste. It is therefore possible that under normal conditions, during digestion of proteins and absorption of the products formed, and also of Glu present in the free form in the diet, through glutathione formation Glu may act on gastric secretion. Glutathione transport with the blood plasma from the liver to other organs and, in particular, to the kidneys is a well known process [8]. Similar transfer may also take place within the digestive system, more especially because increased excretion of glutathione from the intestine into the blood during the absorptive period has been known for a long time [5].

On the basis of the investigations described above it can be postulated that glutathione, formed in the intestine under the influence of Glu and, perhaps, of certain other amino acids also, plays the role of an agent involved in the regulation of gastric secretion particularly of its third phase which is so important for the maintenance of intestinal digestion.

It is interesting to note that the hormone of the third phase, namely entero-oxyntin (not yet identified, but already quite well studied) likewise does not so much have a direct stimulating action, but rather potentiates gastric secretion induced by gastrin [4].

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