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Taras Shevchenko National University of Kyiv
Department of Pharmaco-Physiology of Biology Faculty

TETYANA FALALYEYEVA, TETYANA BEREGOVA,
VITALIY KUKHARSKY

The contrast effect of blocker of AMPA/KA glutamate receptors IEM 1751 on stimulated gastric acid secretion by pentagastrin and histamine in rats

Wpływ blokera receptorów AMPA/KA glutaminianu – IEM 1751 na stymulowane pentagastryną i histaminą wydzielanie kwasu żołądkowego u szczurów

It is well known that glutamate is the major excitatory neurotransmitter of the brain [1, 8]. But the data about the role of glutamate in the peripheral nervous system are limited [7]. In our opinion, in this problem the question about the role of different types of glutamate receptors (central and peripheral) in regulation of gastric acid secretion (GAS) has special importance because pathogenesis of some diseases is connected with disturbances of GAS. Knowledge of the mechanism of gastric acid regulation will allow us to develop new approaches to the treatment of acid dependent diseases. It was established that glutamate acting on AMPA/KA glutamate receptors in the central nervous system intensified basal GAS [4, 6, 10, 11] but glutamate acting on AMPA/KA glutamate receptors in enteric nervous system suppressed basal GAS [4]. Both central and peripheral AMPA/KA glutamate receptors suppressed GAS evoked by cholinomimetic [5, 9].

The aim of the study was to investigate the role of the central and peripheral AMPA/KA glutamate receptors in regulation of GAS stimulated by pentagastrin and histamine in rats.

MATERIAL AND METHODS

The study was carried out in acute experiments on 71 white rats under urethane anesthesia (1.10 g/kg, intraperitoneally (i.p.)). The animals were divided into two groups: I–rats with intact nervous system (INS); II–rats after operation of the bilateral vagotomy which was done at cervical level. GAS was investigated using the method of isolated stomach perfusion by Ghosh and Shild [2]. We studied the influence of antagonist of central and peripheral AMPA/KA glutamate receptors IEM 1751 (5 mg/kg, i.p.) [3] on GAS stimulated by pentagastrin (26 μg/kg, i.p.) and histamine (3 mg/kg, i.p.). The use of rats with the bilateral vagotomy allows us to investigate the role of peripheral AMPA/KA glutamate receptors in the regulation of basal GAS. The samples of perfusate were collected each 10-minutes for 2 hours. Acid output was determined by titration of the perfusate with 0.01 N NaOH to pH 7.0. Our data by Shapiro-Wilks' W test were normally distributed. All results are expressed as the M±SD of n values. Statistical comparisons between groups were conducted using the Student's t-test for unpaired data. Statistical significance was set at $p<0.05$.

RESULTS

In rats with INS antagonist of AMPA/KA glutamate receptors IEM 1751 did not influence GAS stimulated by pentagastrin. However, in rats with bilateral vagotomy IEM 1751 enhanced the total acid secretion stimulated by pentagastrin by 40%, $p<0.05$. Thus, combined blockade of central and peripheral AMPA/KA glutamate receptors did not influence GAS stimulated by pentagastrin. But blockade of peripheral AMPA/KA glutamate receptors leads to the enhancing of pentagastrin GAS. Next, we investigated the influence of IEM 1751 on GAS stimulated by histamine. IEM 1751 had no effect on GAS stimulated by histamine in rats with INS but enhanced histamine GAS in rats after bilateral vagotomy by 81%, ($p<0.01$) (Table 1).

Table 1. The influence of antagonist of central and peripheral AMPA/KA glutamate receptors IEM 1751 (5 mg/kg, i.p.) on gastric acid secretion stimulated by pentagastrin (26 μg/kg, i.p.) and histamine (3 mg/kg, i.p.)

	Pentagastrin	Pentagastrin+ IEM 1751	Histamine	Histamine+ IEM 1751
	Output of gastric acid (μM/120 min)			
Rats with INS	64.3±9.89 (n=10)	66.5±8.91 (n=10)	72.1±12.27 (n=7)	73.52±8.62 (n=10)
Rats after vagotomy	79.54±25.60 (n=9)	111.1±35.9* (n=9)	55.42±8.75 (n=7)	100.5±32.68## (n=9)

Data are means ± SD, n – number of animals, * $p<0.05$ comparison to pentagastrin, ## - $p<0.01$ comparison to histamine

Our results indicate that joint activation of central and peripheral AMPA/KA glutamate receptors by endogenous glutamate does not influence GAS stimulated by pentagastrin and histamine. But central and peripheral AMPA/KA glutamate receptors are involved in the regulation of stimulated GAS by different ways. The excitement of peripheral AMPA/KA glutamate receptors by endogenous glutamate leads to a decrease of pentagastrin and histamine GAS and excitement of central AMPA/KA glutamate receptors by endogenous glutamate leads to the increase of pentagastrin and histamine GAS.

DISCUSSION

In rats with INS antagonist of central and peripheral AMPA/KA glutamate receptors IEM 1751 did not influence GAS stimulated by pentagastrin and histamine. Thus, in natural conditions the excitement of AMPA/KA glutamate receptors by endogenous glutamate both in CNS and ENS do not change pentagastrin and histamine GAS. After vagotomy which removes the action of central AMPA/KA glutamate receptors on GAS IEM 1751 enhanced pentagastrin and histamine GAS. It is a result of blockade of peripheral AMPA/KA glutamate receptors which are activated by endogenous glutamate. The result of this activation is a decrease of pentagastrin and histamine GAS. Absence of effect of IEM 1751 on GAS in rats with INS indicates excitement of central AMPA/KA glutamate receptors by endogenous glutamate has a stimulatory effect on GAS in comparison to the activation of peripheral AMPA/KA glutamate receptors.

Thus, we can conclude that excitement of central and peripheral AMPA/KA glutamate receptors has an opposite effect on GAS: activation of central AMPA/KA glutamate receptors leads to an increase of pentagastrin and histamine GAS but activation of peripheral AMPA/KA glutamate receptors leads to a decrease of pentagastrin and histamine GAS.

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SUMMARY

In acute experiments on 71 white rats by the method of isolated stomach perfusion by Ghosh and Schild it was established that in rats with an intact nervous system antagonist of central and peripheral AMPA/KA glutamate receptors IEM 1751 did not influence gastric acid secretion (GAS) stimulated by pentagastrin and histamine. In rats after vagotomy IEM 1751 enhanced GAS stimulated by pentagastrin and histamine. We concluded that the excitement of central and peripheral AMPA/KA glutamate receptors had an opposite effect on GAS: activation of central AMPA/KA glutamate receptors leads to an increase of pentagastrin and histamine GAS but activation of peripheral AMPA/KA glutamate receptors leads to a decrease of pentagastrin and histamine GAS. In rats with an intact nervous system IEM 1751 did not influence GAS stimulated by pentagastrin and histamine because we deal with a simultaneous action of IEM 1751 on central and peripheral AMPA/KA glutamate receptors which are activated by endogenous glutamate.

STRESZCZENIE

W badaniu przeprowadzonym na 71 szczurach z zastosowaniem metody izolowanej perfuzji żołądka wg Ghosha i Schilda wykazano, że u szczurów z nieuszkodzonych układem nerwowym anatagonista centralnych i obwodowych receptorów glutaminianowych AMPA/KA – IEM 1751 nie wpływa na wydzielanie kwasu żołądkowego stymulowane pentagastryną i histaminą. IEM 1751 zwiększa natomiast wydzielanie soku żołądkowego u szczurów po zabiegu wagotomii. Stwierdzono, że pobudzenie centralnych i obwodowych receptorów glutaminianowych AMPA/KA ma efekt przeciwny. Aktywacja centralnych receptorów prowadzi do wzrostu indukowanego pentagastryną i histaminą wydzielania kwasu żołądkowego, zaś pobudzenie receptorów obwodowych zmniejsza jego wydzielanie. Brak wpływu IEM 1751 na wydzielanie soku żołądkowego w badanej grupie szczurów wynikał najprawdopodobniej z jednoczesnego jego działania na receptory centralne i obwodowe.