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The role of glutamic acid in the regulation of rabbit adrenal activity in the secretion of catecholamines – preliminary research*

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Glutamic acid is the most important excitatory neurotransmitter in the central nervous system. It plays an important role in many physiological processes, such as the development of neurons, synaptic connections, or conduction of nerve impulses. The aim of the study was to determine the effect of glutamic acid in vitro on the activity of the adrenal glands of rabbits in the secretion of catecholamines. The results of the studies described in this work have shown the inhibitory effect of glutamic acid on the secretion of both catecholamines from the adrenal tissue. The lack of dose dependence in the release of noradrenaline as well as adrenaline found in our own research suggests that glutamic acid modulates, in a concentration-dependent manner, hormonal adrenal function. Inactivation of NMDA (ionotropic) receptors for glutamic acid in the adrenal tissue of rabbits by the use of an antagonist of these receptors – ketamine has shown that this type of receptor in the adrenal glands controls to a lesser extent the activity of these endocrine glands under basal conditions. The results of our own research indicate that the use of ketamine in anesthesia does not interfere with the adrenal hormone function in the secretion of noradrenaline and adrenaline.

Key words: glutamic acid, catecholamines, adrenal glands

Homeostasis, defined as the ability to maintain a relatively stable internal state, is a key component of normal body function. The main function of homeostasis is to control and regulate life processes. One of the principal regulatory mechanisms is the nervous system and the released mediators, not only in the central but also in the peripheral nervous system.

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Glutamic acid (Glu) is the most important excitatory neurotransmitter in the central nervous system, with a wide spectrum of activities (Gass and Olive, 2008). It is involved in neuron maturation by regulating their proliferation and migration processes during nervous system development, and is essential for the normal function of this system throughout the life span (Lujan et al., 2005; Gass and Olive, 2008). Glutamic acid acts on target cells in both the central and peripheral nervous system through two receptor types – ionotropic and metabotropic. The former include NMDA (*N*-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole proprionate) and kainate receptors, which control the flow of calcium, sodium and potassium ions. Metabotropic receptors are classified into three subgroups according to the similarity of amino acid sequences (Kania and Wrońska, 2016). Cerebral ammonia accumulation is especially harmful to the body as it inhibits the memorization processes; another important function of glutamic acid is that it binds and removes ammonia from the brain through the blood–brain barrier (Beck et al., 2007). Glutamic acid is also an essential component of protoplasm nerve cells, stimulates the release of pancreatic enzymes, indirectly enhances the absorption of dietary proteins as well as the body's digestive activities (Sills and Loo, 1998).

Ketamine, a non-specific antagonist of glutamatergic ionotropic receptors has been used for several decades in clinical practice as an analgesic and, in large doses, as an anesthetic. This drug increases dopamine activity, stimulates the reward system in the brain, but also has analgesic and antidepressant effects in humans and has been used in addiction treatment therapy (Wolff and Winstock, 2006).

Stress factors of various origins always disrupt basic bodily functions, and, when prolonged in time, they may pose a threat to homeostasis. Of fundamental importance in the body's reaction to stress are the sympathetic–adrenal system (SAS) and the neuroendocrine hypothalamic–pituitary–adrenal axis (HPA) (Carrasco and Van de Kar, 2003). The activity of the former induces the synthesis of catecholamines (adrenaline, noradrenaline), which are the first line of adaptive response to restore the relative balance of the body (Gunnar and Quevedo, 2007).

The adrenal medulla, where both catecholamines are synthesized, is an endocrine gland that releases hormones directly into the bloodstream in response to stimulation of preganglionic sympathetic nerve fibres. Noradrenaline (NA) is the main neurotransmitter essential for signalling between postganglionic nerve cells and effector organs, while it was conclusively indicated that the amount of adrenaline released from the adrenals is considerably greater compared to noradrenaline (Eisenhofer et al., 2004; Arnsten and Li, 2005). These two hormones contribute to stimulating the body to fight-or-flight response in stress situations, thus initiating the metabolic adaptation processes

when the body's homeostasis is disrupted. They increase the heart rate, blood pressure, cause papillary and bronchial dilation. They increase blood glucose concentration due to increased liver glycogen breakdown, as well as indirectly modulating adrenal activity in releasing the adrenal cortex hormones glucocorticosteroids, the properties of which also facilitate adaptation to altered ambient conditions (Rosol et al., 2001; Moryś et al., 2005).

In light of the above facts concerning the properties of glutamic acid, it is of interest to determine its contribution to regulating adrenal activity in noradrenaline and adrenaline release, especially since these three mediators are also found in the central nervous system. The aim of the study was to determine under *in vitro* conditions the amount of two catecholamines (noradrenaline and adrenaline) released into the incubation medium from rabbit adrenal tissue following the use of three doses of glutamic acid, and also after inhibiting the activity of ionotropic receptors for this neurotransmitter.

Material and methods

The experiment involved 7 Popielno White female rabbits aged 12 weeks. Animals were kept in special wooden cages from birth to the start of the trial. At first they stayed with their mothers, and after weaning on day 35 they were housed in individual battery cages. Water and feed (DeHeus complete commercial mixture appropriate for does' age) were available *ad libitum*. The lighting schedule was 10D:14L. Test material (adrenal tissue) was provided by the Department of Genetics and Methods for Improvement of Animals, the University of Agriculture in Krakow. Rabbits were decapitated and the harvested adrenals were placed on ice in Petri dishes containing physiological saline solution. The adrenals collected from each rabbit were cut into smaller pieces of similar weight (around 50 mg), which included the cortical and medullary layers of this gland. The fragmented pieces (sections) of adrenal tissue were placed in incubation wells (Sigma cell culture) containing 1 ml of incubation medium (Krebs phosphate buffer supplemented with 0.3% glucose and 0.1% BSA). Tissues were incubated under carbogen atmosphere (95% O_2 and 5% CO_2) at 38°C in an incubator (MCO-18AIC, Sanyo). Adrenal tissue sections were stabilized for 10 min and transferred to consecutive wells containing pure Krebs buffer as well as 3 different doses of glutamic acid (L-glutamic acid monosodium salt hydrate; Sigma): I – 5 μM, II – 50 μM, III – 200 μM in 1 ml of Krebs buffer. Sections incubated only in pure Krebs buffer served as control. Each adrenal section in the control and experimental groups was transferred to different incubation wells at 30-minute intervals. The control and experimental group medium collected from the wells after 30, 60 and 90 minutes of rabbit adrenal tissue incubation was frozen until analysis. The next adrenal tissue sections harvested from each rabbit were placed in incubation wells containing

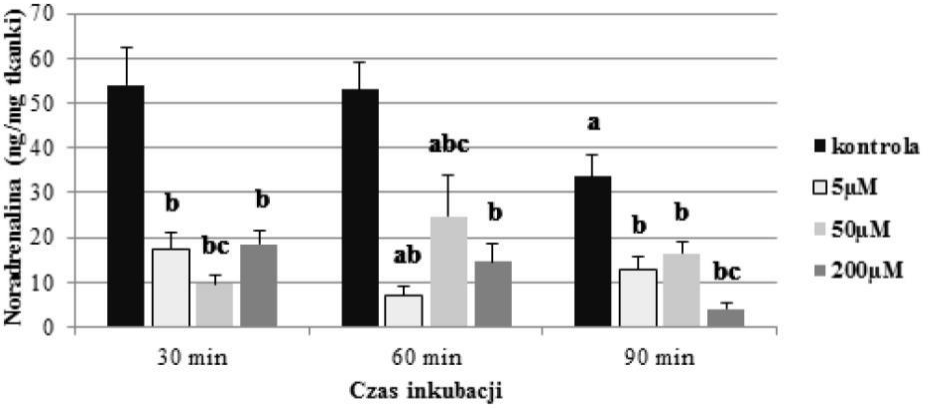
1 ml of Krebs buffer with 3 doses of ketamine: I – 1 μM, II – 10 μM and III – 20 μM (Bioketan, Vetoquinol S.A., Magny-Vernois, BP 189, 70200 Lure, France); preincubation time was 60 min and as previously, each adrenal tissue section was transferred to different incubation wells at 30-minute intervals. The control and experimental group medium collected from the wells after 30, 60 and 90 minutes of the trial was frozen until further analysis. The concentration of catecholamines (adrenaline and noradrenaline) was determined by radioimmunoassay (RIA) using commercial kits (2-CAT Fast Track, Labor Diagnostika Nord, Germany). Sensitivity of the catecholamine determination method was 19 pg/ml for adrenaline, with intra-series error of 8.8% and inter-series error of 10.1%. The respective values for noradrenaline were 42 pg/ml, 10.9% and 123%. The obtained results were converted into 1 mg of adrenal tissue.

Statistical analysis

The results were statistically analysed using two-way analysis of variance in a completely randomized block design. Significant differences between the means were determined with Duncan's test. The calculations were made with SigmaStat 2.03 (SPSS Science Software GmbH, Germany). Differences between the means were significant and highly significant at probabilities of 0.05 and 0.01, respectively.

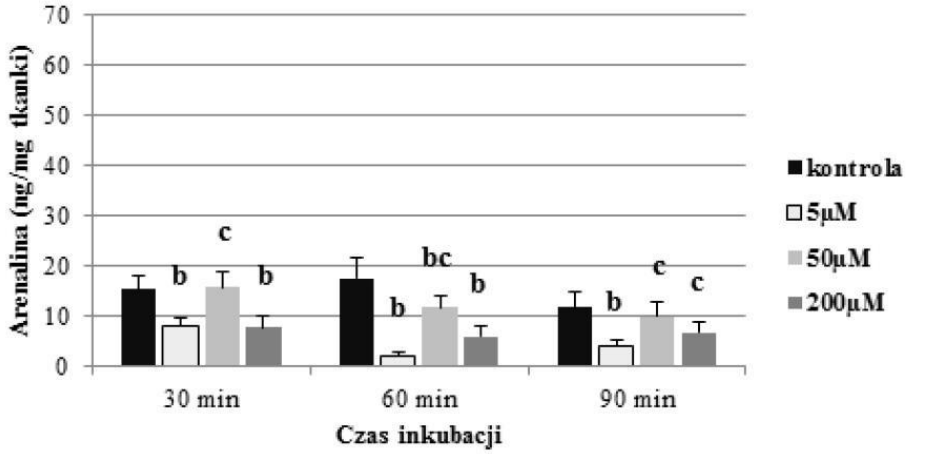
Results

During incubation of rabbit adrenal tissue in pure Krebs buffer, no changes in the amount of adrenaline released during the first 60 minutes of the trial were observed and the values were highly similar (54.0±8.4 and 53.0±5.9 ng/mg of tissue, $P>0.05$; Fig. 1). The last measurement at 90 minutes of the trial showed a significant decrease in the amount of released noradrenaline and the value of 33.6±4.8 ng/mg of tissue proved significantly lower than the earlier recorded values ($P<0.01$). The use of 5 μM glutamic acid for incubation caused a significant reduction in noradrenaline release into incubation medium, and the value of 17.3±3.8 ng/mg of tissue observed at 30 min of the trial was significantly lower than the respective value noted in the control group ($P<0.01$). Over the next 30 minutes, the amount of released noradrenaline continued to decrease, reaching 7.1±2.1 ng/mg of adrenal tissue ($P<0.01$). The last measurement after 90 min of incubation showed an increase in the secretion of this catecholamine (12.7±3.1 ng/mg of tissue). This value continued to be lower than the control value ($P<0.01$). The 50 μM dose of glutamic acid added to the incubation medium caused after the first 30 minutes a more than 5-fold decrease in the amount of released noradrenaline compared to the control value observed during that incubation time (9.6±1.9 ng/mg of tissue; $P<0.01$). It increased significantly over the next 30 minutes (24.6±9.1 ng/mg of tissue; $P<0.01$), and decreased to 16.4 ng/mg of tissue after 90 minutes. All the values noted in this group were significantly different ($P<0.01$).



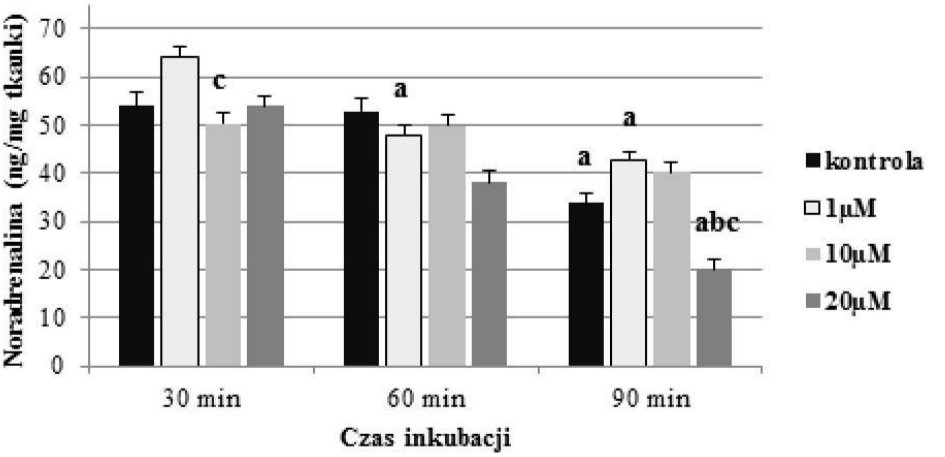
a – values are significantly different (P<0.01) from values determined after 30 min of incubation
b – values are significantly different (P<0.01) from control values
c – values are significantly different (P<0.01) between experimental groups in a given time.

Fig. 1. Effect of glutamic acid on noradrenaline secretion from rabbit adrenal tissue



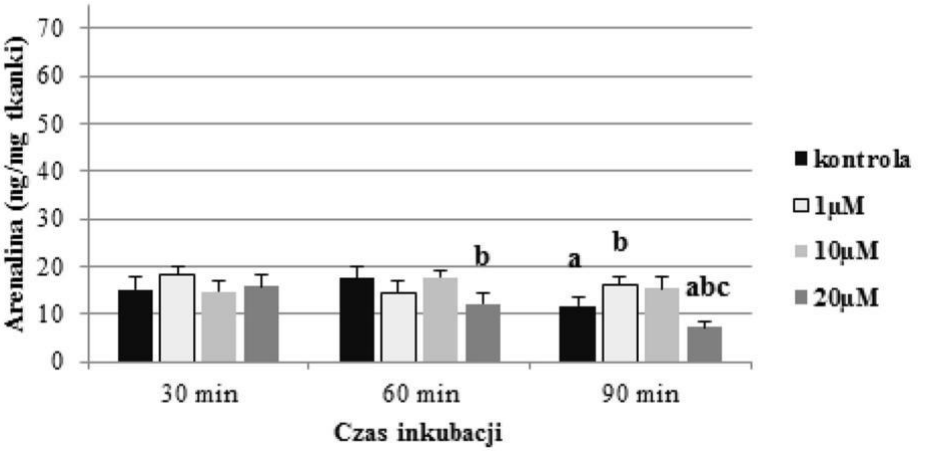
b – wartości istotne różne (P<0,01) w porównaniu z wartością w grupie kontrolnej.
c – wartości istotne różnie (P<0,01) pomiędzy grupami doświadczalnymi w danym czasie.
b – values are significantly different (P<0.01) from control values
c – values are significantly different (P<0.01) between experimental groups in a given time.

Fig. 2. Effect of glutamic acid on adrenaline secretion from rabbit adrenal tissue



a – values are significantly different (P<0.01) from values determined after 30 min of incubation.
b – values are significantly different (P<0.01) from control values.
c – values are significantly different (P<0.01) between experimental groups in a given time.

Fig. 3. Effect of ketamine on noradrenaline secretion from rabbit adrenal tissue



a – values are significantly different (P<0.01) from values determined after 30 min of incubation
b – values are significantly different (P<0.01) from control values
c – values are significantly different (P<0.01) between experimental groups in a given time.

Fig. 4. Effect of ketamine on adrenaline secretion from rabbit adrenal tissue

The highest dose of glutamic acid (200 μM), similarly to the other experimental groups, caused a decrease in the amount of noradrenaline released into the incubation medium. During the 90-minute trial, the secretion of this catecholamine gradually decreased from 18.5 ± 3.1 to 4.0 ± 1.2 ng/mg of tissue. Only the value determined at the last measurement (90 min) proved significantly lower compared to the values determined after 30 and 60 minutes ($P<0.01$). The adrenaline release profile of rabbit adrenal tissue, following the use of glutamic acid, is shown in Figure 2. There were no significant changes in the amount of adrenaline released into the incubation medium in the control group ($P>0.05$).

The use of 5 μM glutamic acid caused a reduction in the amount of released adrenaline. The observed values (15.4 ± 2.8 after 30 min, 17.6 ± 4.2 after 60 min, 11.8 ng/mg of tissue after 90 min) were significantly lower than those in the control group ($P<0.01$). The higher dose of glutamic acid (50 μM) had the least effect on inhibiting the secretion of this catecholamine, and only the value observed after 60 min of incubation was significantly lower compared to the control values ($P<0.01$). The dose of 200 μM also reduced the amount of adrenaline released from rabbit adrenal tissue, the observed values (7.7 ± 2.2 after 30 min, 6.0 ± 1.9 after 60 min, 6.8 ± 2.0 ng/mg of tissue after 90 min) did not differ significantly ($P>0.05$), and only the value observed after 90 min did not differ significantly from that noted at the same time point in the control group ($P>0.05$).

The use of three doses of ketamine (1, 10 and 20 μM) for incubation of rabbit adrenal tissue caused no significant changes in the amount of released noradrenaline after 60 min of the trial compared to the values determined in the control group; it was only after 90 min of the trial that the values noted in the control group and three experimental groups proved significantly lower compared to those determined after 30 min of the trial. In addition, the highest dose of ketamine (20 μM) caused a significant reduction in the amount of secreted noradrenaline compared to all the other groups ($P<0.01$; Fig. 3). The amount of adrenaline released into the incubation medium after the application of three ketamine doses is presented in Figure 4. In the control group, non-significant differences were observed (15.4 ± 2.5 after 30 min, 17.6 ± 2.3 after 60 min, 11.8 ± 1.9 ng/mg of tissue after 90 min; $P>0.05$). No significant differences were found in the amount of adrenaline released in all the experimental groups compared to the control group after the first 60 min of the trial. Only after 90 minutes was the value determined in the 1 μM group significantly higher than in the control group (11.8 ± 1.9 vs 16.6 ± 1.9 ng/mg of tissue; $P<0.05$), while the amount determined in the group treated with 20 μM during that incubation time was significantly lower than in all the other groups (7.2 ± 1.0 ng/mg of tissue; $P<0.01$).

Discussion

The results of the present *in vitro* experiment, conducted with adrenal tissue harvested from rabbits, showed that glutamic acid, the main excitatory mediator of the nervous system, also reaches this endocrine organ and modulates the release of catecholamines.

Glutamic acid plays a major role in the physiological and pathophysiological processes such as the development of neurons and synaptic connections. It is also associated with emotional states, and through the contact with other neurotransmitters it plays major functions in the central nervous system (Maciejak et al., 2001). Glutamic acid activity is determined mostly by the presence of specific receptors which allow it to affect target cells in a given organ; such receptors were also identified in the adrenals (Felizola et al., 2014; Evanson and Herman, 2015). Glutamic acid acts on target cells through two receptor types – iono- and metabotropic. The most important receptor of the glutamatergic system is the NMDA receptor, and chronic stimulation of this receptor for a prolonged time in strong doses may contribute to neuronal damage (Garcia et al., 2009).

While noradrenaline and dopamine are synthesized both in the central nervous system and in the adrenal medulla, adrenaline in mammals is synthesized mainly in the adrenal medulla (Eisenhofer et al., 2004). Noradrenaline is released into the synaptic cleft, from where it is largely taken up by presynaptic terminals and extraneuronal cells, where it is stored (Dziedzic et al., 2008). It can therefore be assumed that glutamic acid, by activating the HPA axis, will also affect the sympathetic-adrenal system (Eisenhofer et al., 2004).

The results of the current experiment showed a decrease in noradrenaline release from rabbit adrenal medullary tissue in response to glutamic acid. *In vitro* treatment of adrenal medullary tissue with glutamic acid at 30-minute intervals showed that the amount of noradrenaline releeased into the incubation medium decreased almost two-fold at each measurement time point, when compared to the respective values determined in the control group. Glumatic acid was found to affect noradrenaline release, but the effect was inconsistent and not dose-dependent. The 5 μM dose of glutamic acid shows a similar effect on noradrenaline secretion as the 200 μM dose (Fig. 1). The present results for the effect of glutamic acid on adrenaline release from the adrenal medulla demonstrated that adrenal medullary activity was inhibited the least by the 50 μM dose of glutamic acid (Fig. 2). When the lowest dose of glutamic acid (5 μM) was used, adrenaline secretion decreased two-fold in relation to the control value; after 1 h the amount of adrenaline released into the incubation medium decreased almost 8-fold in relation to the control and remained unchanged until the end of the trial. The use of the 50 μM dose in the initial stage of incubation did not decrease adrenaline secretion and there was only a slight trend for increased secretion of this catecholamine in response to this dose of glutamic acid. When the 200 μM dose was applied, adrenaline secretion decreased two-fold and remained at this level in relation to the control. After 60 minutes of incubation, adrenaline secretion in response to glutamic acid decreased two-fold to increase again after 90 minutes.

No literature is available regarding the effect of glutamic acid on noradrenaline release from nerve endings of the peripheral noradrenergic system. In the present trial, attention should be given to the clear reduction in noradrenaline release from the adrenal medulla in response to glutamic acid. The comparison made by the authors for noradrenaline secretion under the influence of the major antagonist ketamine, gives insight into the potential effect of glutamic acid in relation to noradrenaline from the central nervous system. One striking observation is the effect of the 50 μM dose of glutamic acid in secreting both noradrenaline and adrenaline, which has the least effect on inhibiting adrenaline release. This can be explained by the fact that glutamic acid activity is determined by its concentration, while also suggesting that activity of a given organ is regulated by the occurrence of a specific concentration of the active substance. Obviously, similar proportions of released noradrenaline and adrenaline are noticeable. It can be also observed that the level of noradrenaline release is around 3–4-fold higher compared to adrenaline, the main hormone resulting from the hormonal activity of the adrenal medulla. In the present trial, we observed that, as expected, the 50 μM dose has a distinctly stimulating effect, and when the highest dose was applied, the inhibitory effect was probably due to the action of endogenous mechanisms that prevent overstimulation of this gland, indeed the toxicity of this mediator.

To determine the impact of glutamic acid on adrenals, its main antagonist ketamine (inhibition of NMDA receptor activity) was used (Javitt, 2004). Many publications have shown that adrenal medullary hormones are a factor affecting ketamine activity in the body (Launo et al., 2004). Ketamine is a substance used as an analgesic in small doses, and in large doses it can be used as an anesthetic in short surgical procedures. It shows analgesic and psychotropic activity, and has a strong effect on the sympathetic nervous system through its inhibitory effect on noradrenaline metabolism and on different cells of the nervous system (Garty et al., 1990; Graf et al., 1995). The inhibitory effect of ketamine has been repeatedly shown with regard to secretion of catecholamines, e.g. after blocking acetylocholine receptors in dog adrenals (Sumikawa et al., 1982), or through the use of agonists of nicotinic receptors in adrenal chromaffin cells of cows (Purifoy and Holz, 1984). A study by Ko et al. (2008) demonstrated a high relationship between the dose and time of intravenous ketamine administration and catecholamine secretion. These results supported the previously proposed theory that secretion of catecholamines is inhibited by antagonists of the nicotinic receptor in adrenal chromaffin cells of cows. Our study revealed no significant differences in noradrenaline release from the adrenal medulla under the influence of ketamine following the use of the lower doses (1 and 10 μM). We believe that the lack of response to the extent of noradrenaline release from the adrenal medulla is due to the fact that catecholin synthesis in the adrenal medulla covers the full pathway from L-tyrosine to adrenaline. The lack of effect on catecholamine release from the adrenal medulla may also result from the inadequate or no stimulation with such ketamine doses of NMDA receptors in the adrenal medulla, for which it is a non-specific antagonist.

The results of the experiment concerning the effect of ketamine on adrenaline secretion showed no difference in the amount of adrenaline released into the incubation medium from the adrenal medulla (Fig. 4). However, it can be observed that the effect of this compound on adrenaline secretion is not dose dependent. Adrenaline secretion in response to low doses of ketamine (1 and 10 μM) does not generally affect its release, although it is apparent that administration of a large ketamine dose (20 μM) reduced by one-thirds the released volume of adrenaline, but the difference is only noticeable after 60-minute incubation of the adrenal medullary tissue. It can therefore be assumed that the use of a high dose of this substance may be toxic to the adrenal medulla and disrupt its activity. Ketamine administration restored the amount of released catecholamines as well as the control values. It can therefore be conjectured that after NDMA receptors are blocked, other receptors will show compensatory activity. Many authors point to the fact that noradrenaline uptake is suppressed in synaptic neural tissues in response to ketamine (Garty et al., 1990; Azzoro and Smith, 1997; Graf et al., 1995).

Lingen et al. (1994) determined the expression and pharmacology of the noradrenaline transporter (NAT) in the cows' adrenal medulla, which is highly similar to that in humans (Pacholczyk et al., 1991). Pharmacological properties of the noradrenaline transporter from the adrenal medulla show a high degree of similarity to the NAT from peripheral noradrenergic neurons, although several essential differences were found, including that the difference in ketamine effect on the level of noradrenaline synthesis and/or release depends on the release site (Bonisch and Bruss, 1994).

Aksoy et al. (2014) described the effect of adrenaline on the duration of action and concentration of ketamine in blood. The results were surprising because in rats receiving a lower dose, which was paralleled by suppression of adrenaline synthesis in the adrenals, adrenaline had a quick effect, whereas 3–4-fold longer action of this antagonist was observed when a higher dose was applied. This experiment provides clear evidence that the effect of ketamine is dose dependent when hormonal activity of the adrenals had been previously suppressed.

Conclusions

The results of the present *in vitro* trial, performed with rabbit adrenal tissue, demonstrated that glutamic acid, the main excitatory mediator of the nervous system, as well as glutamic acid receptors modulate adrenaline and noradrenaline release. The present study involved basal state adrenal tissue which had not been stimulated for example by stress factors, which would alter the hormonal activity of the adrenals, also with regard to catecholamine release. Glutamic acid has been conclusively shown to inhibit the secretion of both catecholamines from adrenal tissue. The lack of dose dependence in noradrenaline and adrenaline release, observed in the present study, suggests that glutamic acid modulates, in a concentration-dependent manner, the hormonal activity of the adrenals. Inactivation of NMDA receptors for glutamic acid in rabbit adrenal tissue through the use of ketamine showed that this type of receptors in adrenals regulates to a lesser extent the activity of these endocrine glands under basal conditions. The present findings indicate that the anesthetic use of ketamine does not disrupt the hormonal activity of the adrenals in noradrenaline and adrenaline secretion.

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The role of glutamic acid in the regulation of rabbit adrenal activity in the secretion of catechola-mines – preliminary research

SUMMARY

Glutamic acid is the most important excitatory neurotransmitter in the central nervous system. It plays an important role in many physiological processes, such as the development of neurons, synaptic connections, or conduction of nerve impulses. The aim of the study was to determine the effect of glutamic acid *in vitro* on the activity of the adrenal glands of rabbits in the secretion of catecholamines. The results of the studies described in this work have shown the inhibitory effect

of glutamic acid on the secretion of both catecholamines from the adrenal tissue. The lack of dose dependence in the release of noradrenaline as well as adrenaline found in our own research suggests that glutamic acid modulates, in a concentration-dependent manner, hormonal adrenal function. Inactivation of NMDA (ionotropic) receptors for glutamic acid in the adrenal tissue of rabbits by the use of an antagonist of these receptors – ketamine has shown that this type of receptor in the adrenal glands controls to a lesser extent the activity of these endocrine glands under basal conditions. The results of our own research indicate that the use of ketamine in anesthesia does not interfere with the adrenal hormone function in the secretion of noradrenaline and adrenaline.

Key words: glutamic acid, catecholamines, adrenal glands