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Glutamate receptors and the airways hyperreactivity

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Abstract. It is proposed the link between the hyperactivity of NMDA receptors and airway hyperresponsiveness. We investigated the effect of agents modulating the activity of NMDA receptors in the ovalbumin-induced airway hyperreactivity in guinea pigs. The airways hyperreactivity was influenced by the agonist (NMDA) and selective antagonist – competitive (AP-5) and non-competitive (MK-801) of NMDA receptors. Airway responsiveness to histamine or acetylcholine was evaluated in *in vitro* conditions. NMDA administration caused the increase of tracheal smooth muscle response in ovalbumin-induced hyperreactivity to acetylcholine. MK-801 as well as AP-5 provoked the decrease of reactivity mainly to acetylcholine in tracheal smooth muscle, while the former, non-competitive antagonist was more effective. We recorded more pronounced response in tracheal than in lung tissue smooth muscle with more considerable response to acetylcholine than to histamine. The results of experiments show the modification of airway smooth muscles responses by agents modulating the activity of NMDA receptors. They confirm the possibility of NMDA receptors participation in experimental airway hyperreactivity. The results enlarge information regarding the link of the inflammatory diseases and glutamatergic system.

Key words: NMDA receptors — Airway hyperreactivity — MK-801 — AP-5

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate; AP-5, DL-2-amino-5-phosphonovaleric acid; CNS, central nervous system; i.p., intraperitoneally; MK-801, dizocilpine; NMDA, N-methyl-D-aspartate; NF-kB, nuclear factor kappa B; ROS, reactive oxygen species.

Introduction

Asthma is characterized with airway obstruction and bronchial hyperresponsiveness to non-specific irritants. Some different hypotheses regarding asthma pathogenesis were pronounced (Gold 1977; Aizawa et al. 1990; Leff 1990), but none of them can explain the diversity of clinical and pathological asthma features. Hoang et al. proposed an interesting hypothesis that asthma is largely due to a hyperexcitatory condition of the airway that is actually kindled in a manner similar to epilepsy, although at first glance asthma and epilepsy don't seem to have much in common: epilepsy is neurological disorder, asthma a breathing problem (Hoang et al. 2006, 2010).

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Then, Hoang et al. (2006) discuss about bronchial epilepsy and they believe that asthma occurs in particular as a result of hyperreactivity of the glutamatergic ionotropic mainly NMDA (N-methyl-D-aspartate) receptors in the airways that bind glutamate. Glutamate is one of the most important excitatory amino acid. In the physiological conditions, it secures the communication between the neuronal cells and plays important role in the brain development, learning, memory or synaptic plasticity. However, the presence of the excessive amount of this neurotransmitter and long-term excessive activation of NMDA receptor act on the neurons unfavourably and can cause even cell apoptosis. This is connected with influx of high calcium amount into cell that triggers the activation of some enzymatic systems (proteinkinases, phospholipases, lipoxygenase, cyclooxygenases, proteases, NO-synthases) and the cascade of reactions that results to formation of reactive oxygen species (ROS). ROS again activate glutamate receptor and cause the tissue injure *via* oxidative stress, evoke lipid and DNA peroxidation,

the activation of caspases, as well as depletion of energetic source that cause cell death (Beal 1992). These processes are responsible for origin of different acute and chronic neurologic diseases with glutamate in the pathogenesis (epilepsy, Parkinson, Alzheimer disease, etc).

Glutamate acts through metabotropic (mGluR) and ionotropic (iGluR) glutamate receptors. The group of metabotropic receptors involves least 8 subtypes linked to G proteins which modulate the activity of different enzymes and ion channels. The group of ionotropic receptors comprises three forms of glutamate receptors: NMDA, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate) and kainate receptors. NMDA receptors are heteromeric complexes comprising of an NR1 subunit combined with one or more NR2 or NR3 subunits. They can exist in the different splice variants and can assign the different physiological and pharmacological properties (Dickman et al. 2004; Waters and Machaalani 2004).

The lung are among the organs outside the central nervous system where some evidence exists for a role for glutamate signalling in physiology as well as in the pathologic states, but where this evidence has been so far incomplete. Said et al. (2001) suppose the presence of glutamate receptors in the lung and airways and also their role in the pathogenesis of acute lung injury and bronchial asthma. They have made further observations that suggest a link between NMDA receptor activation and airway hyperresponsiveness, a cardinal feature of bronchial asthma. Thus, NMDA receptor activation might be important, although still unrecognised mechanism of the airway inflammation and hyperreactivity.

NMDA glutamate toxicity can be susceptible to modulation by intervention at several levels. They include blockade of these receptors by theirs antagonists that can block toxic actions of NMDA activation. We used this intervention for the confirmation of participation NMDA receptors in experimental allergen-induced airways hyperreactivity that simulate situation in human inflammatory respiratory diseases. The task of study is to contribute to the enlargement of knowledge connecting with the glutamatergic NMDA receptor system participation in the airway hyperreactivity conditions.

Materials and Methods

Animals and agents

Pathogens-free adult male Trik strain guinea pigs weighing 200–250 g were used in our experiment. Animals come from approved breeding facility (Department of Toxicology and Breeding of Experimental Animals, Slovak Academy of Sciences, Dobrá Voda, Slovak Republic). Animals were group-housed in individual cages in climate-controlled animal quarters and received water and food ad libitum. Room temperature was maintained at 21 ± 1°C and a 12/12 h light/dark regimen was maintained. The study protocol was approved by the local Ethical Committee of Jessenius Faculty of Medicine (Martin, Slovak Republic). All procedures realized with animals were performed in accordance with internationally accepted recommendations – Helsinki declaration World Medical Association, Direction of European Commission on the protection of animals used for experimental and other scientific purposes (86/609/EHS, 1986) and statute valid in Slovak Republic (Law No. 289/2003 Statute-book Regulation of Slovak Republic).

The three groups of animals treated with agonist or antagonists were used in the experiment:

Group 1: treated with NMDA (agonist of NMDA receptor) in a dose of 4 mg/kg/ml intraperitoneally (i.p.) 30 min prior to ovalbumin administration in 1st, 3rd and 14th day of the sensitization ($n = 8$).

Group 2: treated with selective non-competitive antagonists – dizocilpine (MK-801) in a dose of 1 mg/kg/ml i.p. 30 min prior to ovalbumin administration in 1st, 3rd and 14th day of the sensitization ($n = 8$).

Group 3: treated with selective competitive antagonists – DL-2-amino-5-phosphonovaleric acid (AP-5) in a dose of 4 mg/kg/ml i.p. 30 min prior to ovalbumin administration in 1st, 3rd and 14th day of the sensitization ($n = 8$).

Three control groups were created to each experimental group and received saline 1 ml/kg i.p. prior to ovalbumin administration in 1st, 3rd and 14th day of the sensitization ($n = 8$).

Allergen-induced hyperreactivity

The senzibilization of guinea pigs by allergen (ovalbumin) was used to induce the airways hyperreactivity (Fraňová et al. 2001). The allergen solution (100 μmol of ovalbumin in 1 ml saline) was injected in exact time interval – at the 1st day 0.5 ml administered i.p. and 0.5 ml subcutaneously, at the 3rd day 1 ml was administered i.p. and at the 14th day 1 ml of solution was nebulized and inhaled into the respiratory system. The inhalation of ovalbumin was performed in a body plethysmograph (Hugo Sachs Electronic, type 885, Germany) for rodents and small animals.

Airway responsiveness

Airway responsiveness from control and experimental groups of animals was evaluated in *in vitro* conditions. Animals were euthanized 24 hours after the inhalation of ovalbumin. Strips prepared from trachea and lung tissue were placed into organ bath with Krebs-Henseleit solution

(110.0 mmol/l NaCl, 4.8 mmol/l KCl, 2.35 mmol/l $CaCl_2$, 1.20 mmol/l $MgSO_4$, 1.20 mmol/l $KHPO_4$, 25.0 mmol/l $NaHCO_3$ and glucose 10.00 mmol/l in glass-distilled water). The solution was continuously aerated with mixture of 95% O_2 and 5% CO_2 at pH 7.5 ± 0.1 and temperature 36 ± 0.5°C. The measurement of the reactivity changes was carried out in In vitro Isolated Tissue Bath System (Experimetria Ltd., Hungary). The changes of tension were recorded on a computer with special software. The tissue strips were exposed initially to the tension of 4 g (30 min – loading phase). Then, the tension was readjusted to a baseline of 2 g (30 min – adaptive phase). The Krebs-Henseleit solution was changed every 10 min. The strips contraction was induced by cumulative doses (10^{-8}–10^{-3} mol/l) of histamine or acetylcholine (Sigma Aldrich).

Statistical analysis

All data are expressed as the mean ± S.E.M. The data for each group and differences between the groups were analyzed using the ANOVA test. $p < 0.05$ was considered to be statistically significant.

Results

Figure 1 shows the changes of the airway reactivity in guinea pigs sensitized with ovalbumin (black columns) in comparison with the control animals. Control group was without ovalbumin-induced hyperreactivity (grey columns) and received physiological salt solution instead ovalbumin in equal regimen. Both group of animals treated with NMDA in a dose of 4 mg/kg/ml i.p. 30 min prior to ovalbumin or saline administration in 1st, 3rd and 14th day of the sensitization. The administration of NMDA increased tracheal smooth muscle reactivity to acetylcholine (right side) in ovalbumin-induced hyperreactivity ($p < 0.05$) at the concentration of 10^{-6} and 10^{-4} mol/l, $p < 0.01$ at the concentration of 10^{-8} and 10^{-7} mol/l. The amplitude of tracheal smooth muscle contraction was not significantly changed in histamine (left). Similarly, it was not significantly changed response of lung tissue smooth muscle to both bronchospastic mediators; although response to histamine had the tendency to the fall (data are not shown).

Administration of selective non-competitive antagonist MK-801 in a dose of 1 mg/kg/ml i.p. (white columns) in the equal regimen (30 min prior to ovalbumin administration in 1st, 3rd and 14th day of the sensitization) did not evoke significant difference in the reactivity of tracheal smooth muscle to histamine when we compare the changes with NMDA group (black columns), although it is showed a tendency of decrease in the contraction amplitude in the animals that received MK-801 (Fig. 2).

The selective competitive antagonist AP-5 in a dose of 4 mg/kg/ml i.p. that was administered 30 min before the administration of ovalbumin in 1st, 3rd and 14th day of the sensitization decreased the tracheal smooth muscle response mainly to acetylcholine, statistically significant ($p < 0.05$)

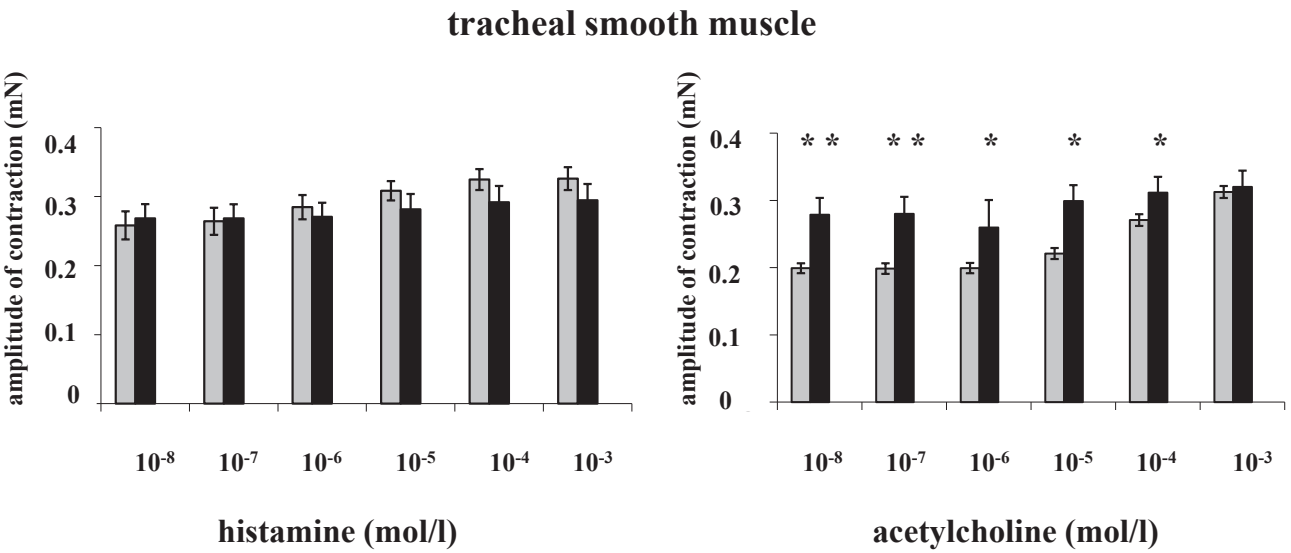

Figure 1. The comparison of the tracheal smooth muscle reactivity changes to histamine (left) or acetylcholine (right) in animal received NMDA in a dose of 4 mg/kg/ml i.p. 30 min prior to ovalbumin (black columns) or saline (control, grey columns) administration in 1st, 3rd and 14th day of the sensitization. The columns represent the average values of the contraction amplitude with mean average ± S.E.M. * $p < 0.05$, ** $p < 0.01$.

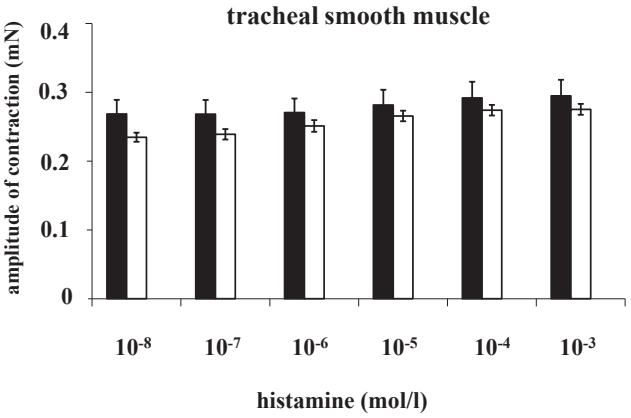

Figure 2. The comparison of effect of pre-treatment with MK-801 in a dose of 1 mg/kg i.p. (white columns) administered 30 min prior to ovalbumin administration in 1st, 3rd and 14th day of the sensitization on the reactivity of tracheal smooth muscle to histamine compared with NMDA group (black columns).

at the concentration of 10^{-8} and 10^{-7} mol/l, sporadically (trachea) to histamine (data are not shown). The effect of AP-5 on the lung tissue smooth muscle for both bronchospastic mediators was not observed.

We show the comparison of the effects of both antagonists (MK-801 – white columns and AP-5 – grey columns) with NMDA group (black columns) on tracheal smooth muscle reactivity to acetylcholine (Fig. 3). Both antagonists evoked on the whole the decrease of the tracheal smooth muscle contraction amplitude when comparing to group with agonist (NMDA). The decrease had showed similar pattern but more expressive statistically significant effect we recorded in selective non-competitive antagonist MK-801.

Fig. 4 represents for illustration the effects of both antagonists (MK-801 – white columns and AP-5 – grey columns) on the lung tissue smooth muscle reactivity in animals with ovalbumin-induced hyperreactivity to acetylcholine comparing with NMDA group (black columns). The response was without statistically significant changes and was nearly identical in all groups of animals.

Discussion

The prevalence of the respiratory inflammatory diseases has the increasing tendency. Thus, it is obvious endeavour to obtain the more information on a pathogenesis of these diseases that subsequently determine orientation on the adequate pharmacotherapy. We endeavoured in our experiment to use new approach supposing that some of these diseases (asthma) and their symptoms (bronchial hyperreactivity) are determined by the hyperexcitatory condition of the respiratory system. Excitatory neurotransmitters (glutamate) and mainly glutamate NMDA receptors activity play here the important role (Said et al. 1999).

Although the NMDA receptor subtypes have been characterized as to their functional roles in the CNS, little is known about the physiologic and pathophysiologic significance of these receptors in the respiratory system. Their up-regulation may be a previously unsuspected mechanism of injury of the lung and other peripheral tissue and organs (da Cunha et al. 2010). The participation of NMDA receptors in the airways reactivity changes has not been widely studied to our knowledge and is only little information regarding the link NMDA receptors and the airways hyperreactivity. Said et al. (2005) showed that the administration of high concentrations of glutamate or glutamate agonist

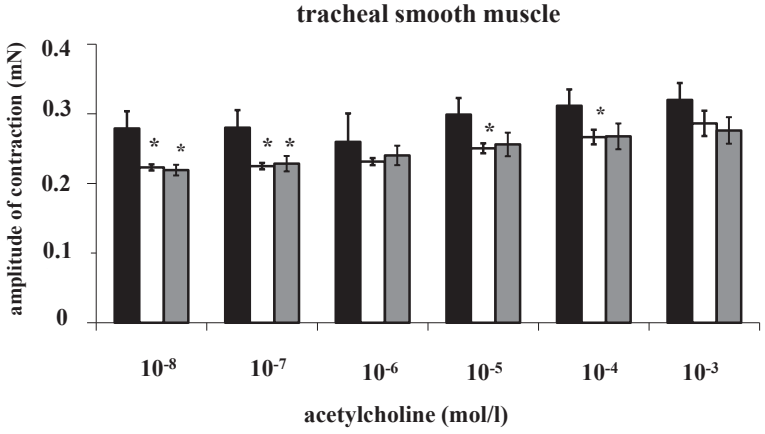

Figure 3. The comparison of effect of pre-treatment with MK-801 in a dose of 1 mg/kg i.p. (white columns) or AP-5 in a dose of 4 mg/kg/ml i.p. (grey columns) administered 30 min prior to ovalbumin administration in 1st, 3rd and 14th day of the sensitization on the reactivity of tracheal smooth muscle to acetylcholine compared with NMDA (black columns) group. * $p < 0.05$.

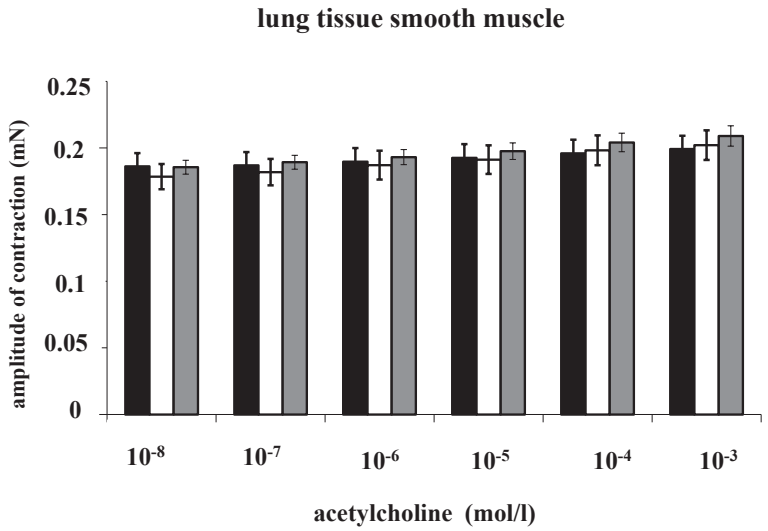

Figure 4. The comparison of effect of pre-treatment with MK-801 in a dose of 1 mg/kg i.p. (white columns) or AP-5 in a dose of 4 mg/kg/ml i.p. (grey columns) administered 30 min prior to ovalbumin administration in 1st, 3rd and 14th day of the sensitization on the reactivity of lung tissue smooth muscle to acetylcholine compared with NMDA group (black columns).

NMDA can elicit acute lung injury with high-permeability pulmonary oedema and airway constriction but molecular mechanism underlying NMDA-induced excitotoxic lung injury had not been elucidated (Shen et al. 2010). Thus, we concentrated in this work on the effect of agents modulating the activity of NMDA receptors as we hypothesize that these receptors may also participate in the pathogenesis of the airways hyperreactivity. We used agonist (NMDA) and antagonists– competitive (AP-5) and non-competitive (MK-801) of NMDA receptors.

The results presented in this study suggest that substances known for their ability to influence glutamatergic receptors in the CNS have pronounced effects on preparations excised from lung. We obtained the changes in the reactivity of airway preparations although mild on the whole. The administration of NMDA prior ovalbumin increased the airways reactivity in guinea pigs compared with animals received NMDA prior saline. This response was more pronounced in tracheal smooth muscle to acetylcholine. The response of tracheal smooth muscle to histamine was without statistically significant changes but using the higher concentration of the mediator we reached a tendency of the decrease. Similar response we recorded in the lung tissue smooth muscle reactivity in all concentration of histamine. This finding is in contrast with the fact that glutamate is excitatory by nature in the CNS and that stimulation of the NMDA receptors in the airway leads in airway constriction (Sato et al. 1998). How to explain our finding? The results of Li and Hatton (2000) suggest that histamine suppresses non-NMDA synaptic currents in some neurons through activation of H_1 receptors. It is possible that histamine induces the production of nitric oxide through activation NO synthase, which modulates response of smooth muscle. Similar results were obtained by Nguyen-Duong (2010) in vascular smooth muscle preparations. Author explains the loss of contractility and reactivity as follows: intracellular calcium overload, stimulation of proteases, protein kinases and phospholipases. The activation of phospholipase A_2 and of cyclooxygenase would generate free-radical species and producing lipid peroxidation and cell damage (Nguyen-Duong 2010). Similar mechanisms might underlie changes in the airways, leading to airway reactivity changes. It is also possible an exercise of the mechanisms independent of the NMDA receptors (Sato et al. 1998). The relaxing effect of NMDA may mimic similar effect of glutamate well-known so-called Chinese restaurant syndrome, which manifests itself as headaches and flushing connected with a vasodilatation (Olney 1990).

More pronounced response to acetylcholine in our experiments may result from some points. NMDA receptors expressed by central structures may play a role in the auto-regulation of presynaptic release and postsynaptic responses to glutamate (Aicher et al. 1999). Haxhiu et al. (1997) suggest that increase in cholinergic outflow to the airways by a variety of reflex excitatory inputs are mainly mediated by glutamate-AMPA receptors that in turn activate the NMDA receptor signalling. In accordance with similar conclusion of Kc and Martin (2010) it is likely that airway sensory stimulation-evoked airway smooth muscle contraction, vasodilatation and hyper-secretion are mediated mainly *via* a cholinergic mechanism, using a glutamate-AMPA signalling pathway that in turn activates

NMDA receptors. Haxhiu et al. (2000) discovered that stimulation of airway sensory receptors by allergen could increase glutamate release in the central structures, producing airway smooth muscle contraction. The repeated activation of broncho-pulmonary sensory receptors resulted in significant glutamate release, which corresponded to increased tracheal pressure indicating that bronchoconstrictive inputs from the airways to central neurons are transmitted primarily by a glutamate receptor signalling pathway. Acetylcholine, as a neurotransmitter involved in central chemo-sensitivity, may facilitate glutamate release on nerve terminals that innervate airway-related vagal preganglionic cells. Corbett et al. (2003) showed that the administration of NMDA antagonist caused a dose-dependent decrease in reflex response of tracheal tone in reflexes evoked by centrally mediated increases in cholinergic tone. Therefore, glutamate-AMPA receptor signalling pathways play a key role in transmitting bronchoconstrictive inputs from the airways to the central structures, where signals are processed, modulated and relayed to the vagal parasympathetic neurons innervating the airways.

The difference in the response of tracheal and lung tissue smooth muscle obtained in our experiments may be connected with different expression and activity of a variety of NMDA glutamate receptor subtypes in the lung and airways as showed in rat Dickman et al. (2004). Their dates propose the expression of NMDAR1 in all regions of the lung and in airways. This subtype is expressed in the airway smooth muscle and constitutively inhibits contraction of isolated tracheal ring in response to acetylcholine (Nassar et al. 2010). NMDAR2D was predominantly expressed in the peripheral regions of the lung. This subtype may be closely associated with lung injury and may also be involved in the mediation of glutamate-induced airway high reactivity and airway inflammation in neonatal rats. Along with prolonging of hyperoxia exposure NMDAR2D mRNA expression was increased (Wang et al. 2009). The same receptors as well as NMDAR2C were expressed in medium-sized and larger airways. These receptors were found in rat peripheral lung including alveolar walls, as well as in bronchial smooth muscle and bronchial epithelium. NMDAR2B is expressed in neurons supplying the upper airways of rat lung (Robertson et al. 1997). The difference in the response of lung areas may be also connected with different localization of other types of receptors (muscarinic, histaminic etc.) or with different activities of the antioxidant mechanisms if ROS are important in the patho-mechanism of the bronchial hyperreactivity. Multiple research groups have reported that excessive NMDA stimulation produces increased levels of nitric oxide and its oxidant product peroxynitrite, which in turn act to both activate and sensitize the NMDA receptors (Pall 2002). Another fact that can play important role in the glutamate receptors sensitivity is the species difference or difference with age as was described by Mallick (2007) in the CNS or the route of administration (Garattini 1979). It is possible that sensitivity, activity or responses of NMDA receptors subtypes as well as like some of these factors could apply in our experimental conditions.

Regarding the probable participation of NMDA receptors in the airways hyperreactivity we assessed the possible modulation of ovalbumin-induced hyperreactivity by the irreversible selective non-competitive NMDA receptor antagonist MK-801 as well as by the selective competitive antagonist of NMDA receptors AP-5. We proposed that these agents could block the excitatory action of NMDA and prevent all manifestations of lung injury induced by NMDA including the airways hyperreactivity. Both agents caused the decrease of the tracheal smooth muscle hyperreactivity induced by ovalbumin more expressive to acetylcholine. The effect to histamine was without statistically significant changes. The activity of both antagonists at level of the lung tissue smooth muscle was also without statistically significant changes but we can see the tendency of the elevation to histamine.

We recorded on the whole more expressive statistically significant effect in MK-801. In the literature date, there are reporting mainly the activity of MK-801 that prevents all manifestations of lung injury induced by exogenous NMDA. This NMDA blocker protects against oxidative stress and limits inflammatory response viewed in lipopolysaccharide-induced acute lung injury (da Cunha et al. 2011). NMDA blockade with MK-801 decreased organism's sensitivity and resistance to hypoxic hypoxia (Tarakanov et al. 2004). MK-801 also significantly inhibited NF-kB expression and the suppression of NF-kB expression inhibited inflammatory mediators and alleviated inflammation and then contributed to the protective effect of MK-801, which may be the intracellular mechanism of the protective effect on hyperoxia-induced lung injury (Tang et al. 2005).

We are fully aware that we cannot pronounce the definitive conclusions on the basis only of these experiments. The problem requires other studies. In summary, in the present study we demonstrated that the activation of NMDA receptors with NMDA caused the increase in the tracheal smooth muscle reactivity to acetylcholine in animals with ovalbumin-induced hyperreactivity. The administration of non-competitive (MK-801) as well as competitive (AP-5) antagonists alleviated ovalbumin-induced hyperreactivity. We suppose that obtained results brought next other knowledge and enlarged information of questions regarding the link of the inflammatory diseases and glutamatergic system.

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