Impairment in pain perception in adult rats treated with N-(-2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP-4) as neonates

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To examine the impact of a central noradrenergic lesion on antinociceptive effects of morphine, paracetamol and nefopam, we compared intact male rats with rats in which noradrenergic nerve terminals were largely destroyed with the neurotoxin DSP-4 [N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine; 50 mg/kg, sc ×2] shortly after birth, on the 1st and 3rd day of postnatal life. When the rats attained 10 weeks of age, painful reactions were assessed by means of the tail immersion test (thermal stimulus) and the paw pressure test (mechanical stimulus). In addition, monoamine levels in some parts of the brain were estimated using the high pressure liquid chromatography with electrochemical detection (HPLC/ED) method. In the tail immersion test, we showed that there were no differences in the antinociceptive effect evoked by morphine (5.0 mg/kg, sc) and paracetamol (100 mg/kg, ip) between control and DSP-4 rats. Nefopam (20 mg/kg, ip) elicited only slight analgesia in control rats (~17%), and this effect was not observed in the DSP-4 treated group; differences were statistically significant at 90 and 120 min of this test. In the paw pressure test we demonstrated that morphine produced lower analgesia in DSP-4 rats in comparison to the control, and the effect was significant at 60, 90 and 120 min of the test. The antinociceptive effect of paracetamol was also greatly diminished in the DSP-4 group and significant in all tested intervals. Nefopam produced only slight analgesia in both tested groups. In biochemical studies we showed that in DSP-4 treated rats there was a marked decrease in NA level in the prefrontal cortex (to 10.4%, p < 0.005), the thalamus with the hypothalamus (to 54.4%, p < 0.005) and the spinal cord (to 12.3%, p < 0.005) in comparison to the control group. Conversely, in the cerebellum and brain stem of rats with DSP-4 lesions there was a significant increase in the NA content vs. control (to 171.2% and 123.5% of NA, respectively, with p < 0.005 and p < 0.05, respectively). In the striatum we did not observe any changes in NA level between the examined groups. The levels of 5-HT and its metabolite 5-HIAA were also not altered by DSP-4 treatment in all tested structures with the exception of the spinal cord (approx. 40% decrease) and the level of DOPAC (also 40% reduction). In conclusion, obtained results showed that neonatal DSP-4 treatment alters the antinociceptive effects of tested drugs (each of them with a different mechanism of action). These data lead to the proposal that perhaps there is a need to adjust the doses of analgesics applied to patients with noradrenergic system dysfunction (e.g., depression and/or anxiety disorders).
Inflammatory and visceral pain perception in rats lesioned with DSP-4 as neonates

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We investigated the reactivity of N-(2-chloroethyl)-N-ethyl-bromobenzylamine lesion (DSP-4; 50 mg/kg, sc × 2, P1 and P3) on the inflammatory and visceral pain perception after morphine, paracetamol and nefopam administration. When rats attained 10 weeks of age, painful reactions were assessed by means of the formalin test (inflammatory stimulus) and the writhing test (chemical stimulus). Furthermore, accumulation of L-dihydroxyphenylalanine (L-DOPA) and 5-hydroxytryptamine (5-HTP) after administration of the aromatic amino acids inhibitor – hydroxybenzylhydrazine (NSD-1015) 100 mg/kg, ip in some part of the brain was examined using high pressure liquid chromatography with the electrochemical detection (HPLC/ED) method. Thirty minutes after a morphine (5.0 mg/kg, sc) challenge, rats were subcutaneously injected into the plantar surface of the right hind paw with 50 µl 5% formalin solution. Both groups showed the typical biphasic nocifensive response curve lasting 60 min of testing but DSP-4 lesioned rats scored more points (spending more time licking/biting the injected hind paw) in the first and second phase as well as the interphase period of the formalin test than the control group. After paracetamol (100 mg/kg, ip) and nefopam (20 mg/kg, ip) administration, typical biphasic nocifensive response curve were also observed; however, no differences between control and DSP-4 treated rats were noticed. Injections of morphine evoked similar antinociception in the visceral pain model in both tested groups (control and DSP-4). Paracetamol elicited lower analgesia in control in comparison to DSP-4 rats; the effect was significant at 20–30, 30–40 and 40–50 min intervals of observation. Nefopam was without effect in this regard. In biochemical assays, equally high levels of 5-HTP in the prefrontal cortex, thalamus with hypothalamus and brainstem were observed when comparing control and DSP-4 lesioned animals (after 0.9% saline). Morphine significantly increased the 5-HTP level only in the prefrontal cortex of control rats. Paracetamol elevated 5-HTP content in the DSP-4 group in the prefrontal cortex but diminished the 5-HTP levels in the thalamus with hypothalamus; at the same time no effect was observed in control animals (in all tested brain parts). Conversely, nefopam decreased 5-HTP content in the prefrontal cortex and thalamus with hypothalamus of DSP-4 rats but no effect was noted in the brain stem. Nefopam did not cause accumulation of 5-HTP in control rats. Equally high levels of L-DOPA in all examined parts of the brain were also noted when comparing control and DSP-4 lesioned animals after saline administration. Morphine did not affect L-DOPA levels in any tested structures of either experimental group of rats. Nefopam reduced L-DOPA only in the brainstem of DSP-4 treated animals in comparison to control (after nefopam administration) and DSP-4 after saline injection. The results of the present study demonstrated that noradrenergic system dysfunction produced by neonatal DSP-4 treatment modified the antinociceptive effects of the examined analgesics.
Influence of imipramine, moclobemide and fluoxetine on pro-inflammatory (TNF-α, IL-1β) and anti-inflammatory (IL-10) cytokines in lipopolysaccharide-stimulated primary rat mixed glial cell cultures

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It is suggested that glial activation and neuroinflammatory processes play an important role in the pathogenesis of psychiatric and neurodegenerative diseases. Activated glial cells secrete various cytokines that influence neurotransmission, HPA axis activity and neuronal plasticity, and may contribute to neuronal cell death.

The anti-inflammatory effects of antidepressants with different influences on monoaminergic systems (imipramine, moclobemide, fluoxetine) were investigated using 13–14 day primary rat mixed glial cultures stimulated by lipopolysaccharide (LPS). Cell cultures were prepared from cerebral hemispheres of one-day old newborn Wistar rats. Levels of TNF-α, IL-1β, and IL-10 were evaluated in culture medium with ELISA kits. The cultures were stained with Ricinus communis agglutinin-1 and an antibody against GFAP. The strongest stimulation of TNF-α release was observed after 6-h incubation with 1 µg/ml of LPS, and for IL-1β and IL-10 after 48-h incubation with 2 µg/ml of LPS. Antidepressants were used in concentrations ranging from 10⁻⁸ to 100 µM. Fluoxetine was only applied at a concentration up to 10 µM because the higher concentration was cytotoxic as determined by MTT and the Trypan Blue exclusion method.

The results have shown that imipramine, moclobemide and fluoxetine decrease TNF-α and IL-1β concentrations in the culture medium but they have no significant influence on IL-10 levels. Moclobemide and fluoxetine reduced TNF-α release at concentrations from 10⁻⁸ to 10 µM. Imipramine produced this effect at concentrations from 10⁻⁸ to 100 µM. Imipramine induced the same effect at concentrations from 10⁻⁶ to 100 µM. Levels of IL-10 did not change significantly after administration of the studied drugs at concentrations from 10⁻⁶ to 100 (or to 10 µM for fluoxetine).

Our results support the observation that antidepressants have anti-inflammatory effects in central nervous system because they affect the balance between pro-and anti-inflammatory cytokines (IL-1β, TNF-α/IL-10) in primary mixed glial cell cultures.

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Influence of baclofen and group I mGluR ligands on activity of rats in the Porsolt test

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Depression is associated with disturbances in transmissions in the glutamatergic and GABAergic systems, producing a misbalance of proper activity in the brain. Data showing the antidepressant activity of ligands for the metabotropic glutamate receptors group I (mGluRs) have been published. A role for
GABA<sub>B</sub> receptors in depression has also been suggested. The cooperation of ligands to receptors in both of these systems is probably important in such pathological condition. The aim of the present study was to investigate the influence of baclofen, a GABA<sub>B</sub> receptors agonist given together with ligands of group I mGluRs, on the activity of rats in the forced swim test (Porsolt test). Imipramine was used as a reference drug. DHPG, an agonist of type I mGluRs and AIDA, MPEP and LY367385, antagonists of mGluR<sub>5</sub>, as well as baclofen, were given ip at the dose of 0.25 mg/kg and markedly shortened the immobility time. A significant shortening in the swimming time was observed after administration of baclofen at the dose 0.5 mg/kg. Baclofen given with DHPG, AIDA or LY367385 had an antidepressant effect in the Porsolt test, similar to that of ligands used alone. MPEP given together with baclofen had no effect on this test.

In conclusion, the obtained results suggest that baclofen activity in this test is dependent upon the dose used. Interaction between an antagonist of mGluR<sub>5</sub> and an agonist of the GABA<sub>B</sub> receptors should be noted.

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Effect of cocaine self-administration on the level of mRNA encoding calcyon in the rat brain

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Calcyon is a transmembrane protein expressed specifically in the rat brain [Zelenin et al., J Comp Neurol, 2002]. It has been shown that to modulate the binding properties of dopamine D<sub>1</sub> receptors and may play a role in intracellular calcium signaling mediated by that receptor [Lidow et al., Eur J Pharmacol, 2001]. Since the dopamine D<sub>1</sub> receptor has been postulated to play a role in the mechanisms of cocaine addiction [Xu et al., Cell, 1994], we therefore decided to study the changes in the level of mRNA encoding calcyon during cocaine self-administration, its withdrawal and reinstatement of a seeking behavior “yoked” procedure [Frankowska et al., Eur J Pharmacol, 2008]. To separate the pharmacological from the motivational actions of cocaine, a “yoked” procedure was employed in which each experimental animal (working actively to get cocaine) was paired with two rats serving as “yoked” controls – one receiving cocaine passively and the other one receiving saline passively.

The level of calcyon mRNA – measured by in situ hybridization – was observed in various brain regions (cortex, caudate putamen, olfactory tubercle, hippocampus, hypothalamus and ventral tegmental area); it was especially high in the paraventricular thalamic nucleus (PVP), arcuate nucleus (ARC), ventromedial hypothalamic nucleus (VHM) and paraventricular nucleus (PVN). That localization was similar to the data provided by Zelenin et al. (2002).

Cocaine self-administration in the first or maintenance phase did not alter the level of calcyon mRNA in the studied brain regions. However, in the animals passively receiving cocaine (“yoked” cocaine control group) a significant increase was observed in the olfactory tubercle (TuOlf). In the hippocampus, the level of calcyon mRNA in all groups was relatively low but well pronounced in the CA1, CA3 and dentate gyrus (DG).

The level of calcyon mRNA in the PVP, ARC, VHM and PVN was higher after the ten day withdrawal period in the cocaine self-administration group passively and actively receiving cocaine as compared to yoked saline controls. It should be noted that in this experimental phase the level of calcyon mRNA in the yoked saline control group was significantly de-
increased in these brain regions as compared to that group in the maintenance phase. In the reinstatement phase of the experiment, cocaine alone induced an increase in the calcyon mRNA expression in most of the brain regions studied (CPu, TuOlf, PVP, VHM and PVN), but only in the yoked saline control group. Interestingly, a similar effect was observed when the reinstatement of cocaine seeking behavior was evoked by cue (conditioned stimuli), indicating that no cocaine was necessary to induce the changes in the level of calcyon mRNA expression. This effect was significant in TuOlf, VHM and PVN. In the reinstatement phase of the experiment in all hippocampal regions studied (CA1, CA3 and DG), cocaine used as a reinforcer decreased the level of calcyon mRNA in the saline yoked group but – in contrast to other brain regions described above – cocaine-evoked reinstatement increased the level of calcyon mRNA in the cocaine self-administering group (in the CA1). It is also interesting that in the hippocampus – in contrast to previously described structures – cue-evoked reinstatement did not induce any changes in the yoked saline group, but did increase calcyon mRNA level in the cocaine self-administering group. The finding that the alterations in the level of calcyon mRNA in the hippocampus in the reinstatement phase was dependent on previous experience with cocaine may point to the role of memory mechanisms operating in that brain region.

What is the influence of long-term isolation on appetitive ultrasound vocalization in rats? A new model of social interaction

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Laboratory rats emit two types of high-frequency vocalizations (aversive and appetitive calls) in a number of behavioral situations. This paper shows the impact of the encounter of pairs of adult rats after long-term isolation on 50-kHz ultrasound vocalizations (USVs). The aim of this study was to establish a new animal model of appetitive behavior and to study the effects of selected psychotropic drugs on aversively – and appetitively evoked ultrasonic vocalization. It was found that the isolation of the adult rats increased the appetitive ultrasound vocalization during the rats’ encounter. Long-term isolation-evoked USVs could also be used as a selective tool to study the central effects of psychotropic agents. It is hypothesized that meeting another known rat after isolation became to be a reward incentive that triggers appetitive behavior such as 55-kHz ultrasound vocalization. The psychological mechanisms involved in this phenomenon are not clear. One of the hypotheses is that isolation reduces the incentives’ rustle intensity, and in consequence the social response is more intensive. The other hypothesis is that isolation makes the animals overreactive to the different social and non-social stimuli. In the pharmacological part of the study it was shown that diazepam increased and tofizopam decreased isolation-induced USVs, and that buspirone had no effect. On the other hand, aversive context-induced USVs (22-kHz) were almost totally abolished by buspirone, but not changed by the pre-treatment of rats with tofizopam. This preliminary pharmacological analysis indicates that different neurochemical mechanisms are probably involved in the control of socially-related and aversive stimuli-evoked USVs (GABAergic vs. serotonergic). Further studies are warranted to explain the phenomenon of isolation-induced USVs.
The role of neuronal nitric oxide synthase in 3,5-DHPG-induced behavioral effects in rats

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In this study, we tested the influence of the agonist of class I metabotropic glutamate receptors (mGluR), (S)-3,5-dihydroxyphenylglycine (3,5-DHPG), on memory motivated affectively (passive avoidance situation) and appetitively (T-maze) after the blockade of neuronal nitric oxide synthase (nNOS) by 7-nitroindazole (7-NI) in rats. Moreover, the speculative influence of treatment on motor activity and anxiety were tested in 'open field' tests and elevated plus mazes. Experiments were performed on male Wistar rats weighing 150–180 g. Inhibition of the nNOS was evoked by ip injection of 7-NI at the dose of 30 mg/kg. Thirty minutes later the animals were given icv solution of 3,5-DHPG at the dose of 25 nmol. We observed that administration of 3,5-DHPG after the learning trial significantly facilitated the consolidation process in a passive avoidance situation, but when given before the retention testing, it did not have any influence on the retrieval process. In the T-maze, 3,5-DHPG failed to change the working memory of rats. Examination of the influence of 3,5-DHPG on motor activity proved that it significantly attenuated crossings squares and rearings, but not bar approaches in an 'open field' test. Similarly, 3,5-DHPG decreased motor activity in the elevated plus maze, scored as a number of arm entries. On the other hand, 3,5-DHPG did not have an influence on the time spent in the open and closed arms (evaluated in this test as the anxious activity).

For the most part, pre-treatment with 7-NI had no influence on 3,5-DHPG-induced behavioral effects on the conducted tasks. Only in an 'open field' test did pre-treatment with 7-NI prevent the decreasing effect of 3,5-DHPG on the number of crossings squares as seen in 3,5-DHPG-separately treated animals. In conclusion, these results suggest that nNOS is likely not involved in the behavioral activity of class I mGluR agonists such 3,5-DHPG.

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The role of the central cholinergic system in the mechanism of the convulsive effect of meso-tetra-4N-methylpyridyl-porphyrin (P)

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Our previous study found that central β-adrenergic receptors are involved in the mechanism of the neurotoxic effect of meso-tetra-4N-methylpyridyl-porphyrin (P) expressed as a convulsive effect. In this report we present the effect of cholinergic receptors on P-induced convulsions. Experiments were performed on Balb mice and female Wistar rats. The convulsive effect of ip injected meso-tetra-4N-methylpyridylporphyrin (P) was determined in mice (ED₅₀ = 54.3 mg/kg). Moreover, the effect of icv-injected meso-tetra4N-methylpyridyl-porphyrin (P) was determined in female rats. The following measures were used to determine this effect either in mice or in rats: the number of animals with seizures, the latency time at the be-
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Prenatal nicotine exposure and convulsive seizures

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Male, 3-day-old Wistar rats were injected with 5,7-DHT 75 g icv. Control rats obtained saline vehicle 10 μl icv. At eight weeks, the level of 5-hydroxytryptamine (5-HT) and 5-hydroxyindolacetic acid (5-HIAA) was estimated in the striata, frontal cortices and hippocampus of the brain using the HPLC/ED technique. Other 8-weeks-old animals of both groups were injected with thioperamide 5.0 mg/kg, ip. Control rats from both groups were injected with saline 1.0 ml/kg, ip. Sixty minutes later 6-[3H]-D-glucose (Amersham) was applied to all rats in a dose of 500 Ci/kg, ip and 15 min later animals were decapitated and their brains were excised, placed on ice and samples of the frontal cortex, striatum, hippocampus, and thalamus with hypothalamus were separated and weighted. The radioactivity of the tissues was then examined and measured using a liquid scintillation counter and expression in DPM/100 mg of wet tissue.

5,7-DHT significantly decreased the levels of 5-HT and 5-HIAA in all examined tissues of the brains of adult rats. In adult rats neonatally lesioned with 5,7-DHT, radioactivity was significantly increased in all examined parts of the brain as compared to the control. Thioperamide diminished observed effect in 5,7-DHT neonatally lesioned rats as compared to respective controls. From the above results, we conclude that there is a functional association between the serotoninergic and histaminergic system in mammalian brains.
Histaminergic activity in adult rats neonatally lesioned with neurotoxins: DSP-4, 5,7-DHT and 6-OHDA (rodent model of Parkinson’s disease)

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Histamine (H) appears to be a neuromodulator, regulating motor activity, awareness, wakefulness, pain and other functions. Histaminergic cell bodies in the brain are located in the hypothalamus, sending diffuse projections to all brain regions and interacting with other neurotransmitter systems. In an effort to study the latter process, the monoaminergic neurotoxins DSP-4, 5,7-dihydroxytryptamine (5,7-DHT) and 6-hydroxydopamine (6-OHDA) were administered to destroy the noradrenergic, serotoninergic and dopaminergic systems in the brains of rats, respectively.

Each neurotoxin was injected in newborn male Wistar rats as follows: DSP-4 (50 mg/kg, sc) on the 1st and 3rd day after birth; 5,7-DHT (75 µg, base, icv) or 6-OHDA (134 µg, base, icv) on the 3rd day after birth. Controls were injected with saline sc or icv, respectively. Adulthood levels of biogenic amines were estimated in the brain by HPLC/ED, and H levels were established by immunoenzymatic methods. In addition, behavioral observations of oral activity and stereotyped behavior induced by SKF 38393 and apomorphine (D1 and D12 agonists, respectively) with or without S(+)-chlorpheniramine (10 mg/kg, ip), cimetidine (5 mg/kg, ip), or thioperamide (5 mg/kg, ip) (H1, H2 and H3 receptor antagonists) were performed.

DSP-4 reduced the adulthood level of norepinephrine and H in the brain, while 5,7-DHT reduced the adulthood level of serotonin and H in the brain. 6-OHDA-lesioned rats had a reduced DA but elevated H levels in the brain. Thioperamide only attenuated SKF 38393-induced oral activity as well as apomorphine-induced stereotyped behavior in 6-OHDA-lesioned adult rats.

The findings indicate that the histaminergic system exerts a modulatory role in the brain of 6-OHDA-lesioned rats via H3 receptors – a model of severe Parkinson’s disease.

Influence of lesions of cerebellar catecholaminergic systems on the harmaline-induced tremor in rats

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Tremor is a rhythmic, involuntary, oscillatory movement of a body part with relatively fixed frequency and amplitude. Tremor may be a physiological reaction or a pathological sign of several neurological disorders, including Parkinson’s disease. Mechanisms underlying both physiological and pathological tremors are poorly understood, although both central oscillators and peripheral reflex mechanisms have been found to be involved.

Harmaline is a well-known tremorgenic substance used to model this symptom in animals. Activation of the glutamatergic pathway arises from the inferior oliv and extends to Purkinje cells of the cerebellar cor-
Inhibition of cyclase GMP-blocked antinociceptive effect of heptapeptide [2-8]-leucopyrokinin ([2-8]-LPK) in rats

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We have found in our previous study that a synthetic, active analog of insect neuropeptide leucopyrokinin (LPK) [2-8]-leucopyrokinin ([2-8]-LPK) exerts a significant antinociceptive effect in rats, mediated by central opioid receptors: µ and δ. Moreover, the role of NO⁺ (which is produced by nitric oxide synthase (NOS)) in the mechanism of [2-8]-LPK-induced analgesia in rats was recently reported.

The present study was undertaken in order to determine a role of cGMP, an end-point of the L-Arg-NO⁺-cGMP pathway, in the mechanism of [2-8]-LPK-induced analgesia. Experiments were performed using adult male Wistar rats. A week before the experiment, animals were anesthetized and polyethylene cannulas were implanted into the right lateral brain ventricle. The antinociceptive effect was determined by a tail immersion test. It was found that icv injection of [2-8]-LPK in two doses of 5 and 10 nmols induced a significant antinociceptive effect. Pre-treating rats with methylene blue, an inhibitor of GMP-cyclase, in equimolar doses of 5 and 10 nmol 30 min before [2-8]-LPK strongly inhibited its antinociceptive effect.

The results of the present study indicate the role of cGMP in the mechanism of the [2]-LPK-induced antinociceptive effect in rats.

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The central (CeA) and basolateral (BLA) nuclei of the amygdala have an important role in regulating anxiety and affective responses. Glutamate (Glu) and gamma-aminobutyric acid (GABA) in the amygdala are thought to be crucial for the acquisition and expression of fear memories. The amygdala also expresses high concentrations of CRF (corticotropin-releasing factor) and CRF receptors. During periods of stress, CRF is released into the amygdala and local CRF receptor activation has been postulated as a substrate for fear-induced alterations in affective behavior. The aim of the study was to examine the effects of intraventricular injections of CRF and a non-selective CRF receptor antagonist, \text{\textalpha}-helical CRF\text{\textsubscript{(9-41)}}, on the freezing reaction in the conditioned fear test and on the release of aspartate, glutamate, and GABA in the central and basolateral nuclei of the amygdala, using microdialysis technique. It was found that pre-treating rats with CRF (1 µg/rat) increased the concentration of aspartate, Glu and Glu/GABA ratio in the CeA and BLA (up to 500% of the baseline value), an effect that appeared 15 min after and that preceded an increased expression of anxiety-like responses, and after drug administration. Intraventricular administration of \text{\textalpha}-helical CRF\text{\textsubscript{(9-41)}} (10 µg/rat) significantly decreased rat freezing responses and increased the local concentration of GABA during the first 30 min of observation. The present data show an enhancement of excitatory processes in the examined part of the amygdala, point to the role of CRF in the integration of central, anxiety-related, biochemical and behavioral responses, and implicate the amygdala amino acids-related innervation in the effects of this neuropeptide.
except that half each of the SAL-pretreated rat groups were given a SAL challenge instead. After the 1st and 14th pretreatment dose, and after the challenge, the rats were tested for open field locomotor activity. Two hours after the challenge, all the rats were killed and the caudate-putamen contents of glutamate, glutamine, aspartate, arginine, glycine, alanine, taurine and GABA were measured. Analysis of behavioral data showed considerable similarities (in total distance covered, TD) and dissimilarities (in the distance covered by the rats in the central part of the open field arena, CD) in the effects of the MF and MET pretreatments. TD data showed locomotor sensitization to the MF challenge only in the WHP rats, both after the MF or MET pre-treatment. CD was considerably affected by the MF pre-treatment, and only that significantly increased it in the WHP rats. The MF challenge significantly decreased striatal contents of glutamate, glutamine and aspartate in SAL-pretreated rats of either strain. This effect was abolished in the MF-pretreated, but not in the MET-pretreated rats. MF-pretreated WLP rats showed markedly higher arginine content after the MF challenge than their SAL-pretreated WLP counterparts or the MF-pretreated MF-challenged WHP rats. We speculate that this difference may result from reduced decarboxylation of arginine to agmatine, the newly discovered neurotransmitter that is believed to hamper the development of tolerance and dependence.

The role of GABAergic transmission in the behavioral effects of mGlu7 receptor positive modulator, AMN082

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Broad evidence indicates that modulation of the glutamatergic and/or GABAergic system could be an efficient way to achieve antidepressant activity. Metabotropic glutamate receptor (mGlu receptor) ligands seem to be promising agents to treat several central nervous system disorders, including depression. Recent investigations brought several communications about the effectiveness of GABA B receptor ligands in animal tests and models detecting antidepressant-like activity of drugs. Antidepressant-like effects were observed for mGlu7 receptor positive modulator, AMN082, as well as for GABA-B receptor antagonists, CGP 51176 and CGP 36742. GABA B receptor antagonist, CGP 44532, was not effective in the test, but it counteracted the antidepressant like effect of CGP 51176. The aim of our study was to investigate if the antidepressant effect of AMN082 in the forced swim test is dependent on GABAergic neurotransmission, mainly through GABA B receptors. AMN082 was administered in two doses: effective 6 mg/kg, and not effective, 3 mg/kg. The not effective dose of AMN082 was investigated together with not effective doses of GABA B receptor antagonists, which in both cases were doses of 5 mg/kg. Combined administration of ineffective doses of mGlu7 receptor modulator and GABA B receptor antagonists did not reveal any antidepressant-like effect in the FST in mice. However, the antidepressant-like activity of AMN082 was completely blocked by the GABA B receptor agonist, CGP 44532 administration, in a dose of 0.250 mg/kg. Results of our studies indicate that the antidepressant-like activity of AMN082 is dependent on GABA acting through GABA B receptors.