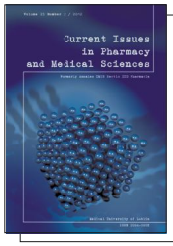

2012 © Curr. Issues Pharm. Med. Sci. Vol. 25, No. 2

Current Issues in Pharmacy and Medical Sciences

Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA
on-line: www.umlub.pl/pharmacy

The role of metabotropic glutamate receptor 7 (mGluR7) in drug dependence

MAŁGORZATA JENDA*, KINGA GAWEŁ, JOLANTA H. KOTLIŃSKA

Department of Pharmacology and Pharmacodynamics, Medical University of Lublin, Poland

ABSTRACT

The successful pharmacotherapy for drug addiction is a challenge for pharmacology in XXI century. We still do not have any registered medication for cocaine by FDA, alcohol therapies are not enough successful. High hopes concern metabotropic glutamate 7 receptor as a target for pharmacotherapy development of drug dependence. It is well documented the role of the mGluR7 in rewarding and motivational effects of cocaine and alcohol. The mGluR7 allosteric agonist AMN082 and antagonist MMPIP have become new tools in preclinical studies. AMN082 attenuated cocaine-enhanced electrical Brain Stimulation Reward (eBSR) in rats and decreased cocaine self-administration too, probably by counteracting cocaine-induced inhibition of the ventral pallidal GABA release. The mGluR7 activation reduced alcohol intake and preference in rats. The mGluR7 receptors take part in reinstatement of drug-seeking behavior after abstinence. The investigations showed that AMN082 suppressed cocaine-induced reinstatement of self-administrated rats via mGluR2/3 mechanism. It was mentioned also that mGluR7 allosteric agonist inhibited reinstatement of ethanol-induced CPP. Moreover, activation of the mGluR7 receptor exhibits less adverse reaction in comparison to other mGluRs and may give a promise for further development of drug dependence therapies in humans. However, some nonspecific effects of the mGluR7 in ethanol addiction have been recognized, so there are further investigations needed to explain the mechanisms of the mGluR7 action in rewarding and motivational effects of drugs.

Keywords: metabotropic glutamate 7 receptor, mGluR7, AMN082, MMPIP

INTRODUCTION

Drug addiction is a chronic disorder characterized by craving and relapse to drug use after abstinence. Dependence occurs due to long-term neuroadaptation that leads to changes in motivational and emotional area of brain function as well as learning memory [32, 53]. Many neurotransmitters are involved in mechanisms of drug addiction e.g. dopamine (DA), noradrenaline, acetylcholine, glutamate (Glu) and others, but interaction between them remains still unclear [26]. The review is focused on recently published data concerning the role of glutamate metabotropic receptors 7 (mGluR7), one of the subtype of group III metabotropic glutamate receptors (mGluRs), in drug addiction.

The glutamate is the most omnipresent excitatory neurotransmitter in the brain which participates in neuroplasticity mediated to long term potentiation, depression, extinction and memory related to reward [11, 36, 61]. It has been recognized that reward processing depends on mesocorticolimbic DA systems, comprising DA neurons in the ventral tegmental area (VTA) and their projections to nucleus accumbens (NAc), amygdala, prefrontal cortex (PFC), and other forebrain regions. However, most drugs of abuse have been shown to stimulate excitatory glutamatergic transmission throughout brain reward circuitries [30, 71]. Increases in glutamatergic transmission have been shown to play an important role in mediating the positive reinforcing actions of addictive drugs [27]. Glutamate acts by two types of receptors: ionotropic and metabotropic. The ionotropic receptors (iGluRs): activated by *N*-methyl-D-aspartate (NMDA), 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid (AMPA) and kainic acid (KA) are mediated to fast action by ion channels while the mGluRs are responsible for slow glutamate responses though G-protein [6]. mGluRs are divided into three groups based on signals transduction mechanisms, sequence homology and pharmacology properties [56]:

- group I: mGluR1 and mGluR5
- group II: mGluR2 and mGluR3
- group III: mGluR4, mGluR6, mGluR7 and mGluR8.

Receptors from group I are primarily located postsynaptically, while group II and III are largely situated presynaptically, acting as inhibitory autoreceptors regulating glutamate releasing or heteroreceptors controlling the release of other neurotransmitters. [51]. The group I receptors (mGluR1 and 5) are responsible for stimulation of phospholipase C which leads to release of Ca^{2+} stores and increased glutamate transmission whereas group II and group III mGluRs inhibit adenylyl cyclase and decrease cAMP conversion leading to a decrease in glutamate transmission [13, 23, 56].

The mGluR7, one of the subtypes of group III mGluRs, is supposed to play very important role in the brain function

Corresponding author
* Department of Pharmacology and Pharmacodynamics, Medical University of Lublin, 4A Chodzki Str., 20-093 Lublin, Poland
e-mail: gosiajenda@tlen.pl

[14], because of being the most conserved receptor subtype among all metabotropic glutamate receptors in mammalian species [22]. It suggests that an effective mGluR7 agent in experimental animals is likely to be effective at human levels [42]. These receptors are largely located presynaptically and act not only as autoreceptors, but also as heteroreceptors to modulate release of ă-aminobutyric acid (GABA) in particular [8, 10]. Generally, the main role of the mGluR7 is modulation of release neurotransmitters. The high density of the mGluR7 in reward-related brain region – the ventral pallidum (VP), NAc, striatum, hippocampus, amygdala, olfactory bulb, suggest the potential role of the mGluR7 in mechanisms of addictive drugs [33]. There is numerous evidence that blockade of both group I mGluRs, mGluR1 and mGluR5 or activation of presynaptic group II mGluR2/3 decrease motivational and rewarding effects of addictive drugs such as cocaine, alcohol, morphine, nicotine [37, 38, 43, 50, 53]. The mGluR7 has been investigated the least among all mGluRs because of long period with no selective agents available. The mGluR7 appears to be involved in the development and extinction of aversion and fear responses [21, 47]. Knockout animal studies as well as pharmacological approaches support the relevance of the mGluR7 receptor for regulation of the hypothalamic-pituitary-adrenal axis (HPA axis) and in mood disorders such as depression and anxiety [9, 17, 49].

AMN082 AND MMPIP AS NEW TOOLS FOR MGLUR7 RESEARCH

In 2005 Mitsukawa et al. [48] identified AMN082 (*N,N'*–dibenzhydrylethane–1,2-diamine dihydrochloride) – selective allosteric agonist of the mGluR7. This discovery was critical for investigation of the role of these receptors in drug dependence. AMN082 activates receptor by allosteric site in the trans-membrane domain, different to extracellular N-terminal domain for orthostetic agent like endogenous glutamate [48]. In the absence of glutamate, this agent is devoid of intrinsic activity [49]. Indirect allosteric activation has the advantages over direct orthrostetic agents due to less adverse reactions, e.g. excessive activation or desensitization of receptors and pulsatile release of neurotransmitter [44]. The influence of AMN082 on glutamate level in the NAc is complicated. On the one hand, AMN082 inhibits non-vesicular NAc Glu release, but on the other hand this agent elevates vesicular Glu level in the NAc by indirect disinhibition mechanism [39]. A detailed description of this action is presented further in this review. AMN082 is orally active and penetrates the blood-brain barrier. It enhances the levels of stress hormones corticosterone and ACTH in wild type mice, but not in the mGluR7 knockouts [48]. AMN082 was reported to induce anxiolytic-like and antidepressant effects, regulate emotion and cognitive processes [21, 54, 63, 64]. However, recently it has turned out that a metabolite of AMN082, Met-1, is a monoamine transport inhibitor. This means that data collected via systemic administration of AMN082 needs to be interpreted with caution due to the potential of effects being mediated through non-mGluR7 receptor mechanisms [65].

The next step in mGluR7 studies development included selection of the new allosteric negative modulator of these receptors, 6-(4-methoxyphenyl)-5-methyl-3-pyridin-4-ylisoxazol[4,5-c]pyridin-4(5H)-one (MMPIP) [66]. This agent penetrates into the brain after systemic administration in mice and rats. Investigation showed that MMPIP selectively impaired cognition process without any influence on locomotor activity, sensorimotor function, emotional responses, nociception in mice and rats [28]. Researchers usually use MMPIP to inverse AMN082 action in vivo to confirm that mGluR7 activation in only one factor in investigating process [2, 3, 40, 41].

Except numerous applications of mGluR7 in neuropsychiatric disorders, these receptors are likely to take part in the development of drug dependence. AMN082 and MMPIP have become useful tools to enable exploration the mGluR7 mechanisms in drug addiction in animals and discovery new medication for humans in future. The investigation has taken two main directions: the mGluR7 in alcohol and psychostimulants dependence, particularly cocaine.

THE MGLUR7 IN COCAINE DEPENDENCE

Despite many research studies and efforts, there is no medication available and approved by the Food and Drug Administration (FDA) for the treatment of cocaine dependence. Lack of success probably results from complicated central effects of cocaine and its potent reinforcing action. The exploration of pharmacological and behavioral effects of cocaine is enabled by animal models of addiction in particular [26].

Li et al. [40] revealed that activation of the mGluR7 by AMN082 inhibited the rewarding effect of cocaine, assessed by electrical brain stimulation reward (eBSR). eBSR is a sensitive animal model to determine the rewarding properties of drug [69]. AMN082 attenuated cocaine-enhanced eBSR in rats. This influence is selective only for cocaine, because of the fact that AMN082, *administered intraperitoneally* (i.p.), induced nor aversive- neither rewarding-like effect on eBSR. Systematic administration as well as intracranial microinjection of AMN082 into the NAc or VP, but not the dorsal striatum, inhibited intravenous cocaine self-administration under both fixed (FR) and progressive-ratio (PR). So AMN082 not only inhibited primary rewarding and motivational effect of cocaine, but also reward-enhancing in PR schedule [42]. It should be noted that AMN082 had no effect on either locomotion or sucrose oral self-administration, suggesting a selective inhibition of cocaine rewarding properties. This effect was blocked by co-administration of MMPIP, suggesting that an effect is mediated by activation of mGluR7s in the NAc-VP pathway. *Additionally,* microdialysis showed that systemic administration of AMN082 changed neither basal nor cocaine-enhanced extracellular

DA in the NAc or VP, but attenuated cocaine-induced inhibition of VP GABA release in both drug naive rats and cocaine self-administration rats. The data suggest that the NAc-VP GABAergic mechanism could contribute to mGluR7 modulation of cocaine reward [40]. There is evidence that the psychostimulant reward is related to the VTA-NAc-VP pathway, including the NAc-VP GABAergic projection [36, 59, 70]. Therefore, any pharmacological strategy that increases GABAergic transmission of reward circuit might directly counteract psychostimulant-induced inhibition of GABAergic neurons. [18, 72].

The previous studies of Li et al. showed that acute systemic and local AMN082 administrations produced decrease of GABA and slow onset, long-term increase of glutamate level in NAc [39]. It is possible that GABA produces inhibitory control over NAc glutamate releasing via presynaptic $GABA_B$ receptors on glutamatergic terminals [64]. On the other hand, the mGluR7 acts either as auto-receptor regulating glutamate releases or as presynaptic heteroreceptor regulating GABA release. In the consequence, AMN082 induces reduction in NAc GABA levels by mGluR7 heteroreceptor. After that, a lower GABA level unblocks the other heteroreceptor $GABA_B$ on glutamatergic synapses. In conclusion, the direct inhibition mechanism by mGluR7 autoreceptors is suppressed by disinhibiting mechanism via $GABA_B$ receptors, resulting in an increase of NAc glutamate release from vesicular sources [39]. These changes of GABA and glutamate level in NAc are supposed to enhance excitability of postsynaptic medium-spiny GABAergic projection neurons that counteract cocaine-induced GABAergic inhibition in the VP [39]. It is consistent with the GABAergic hypothesis of drug reward discussed previously [18, 72].

It is well documented that glutamate transmission in cocaine-dependent individuals is deregulated. High doses of cocaine (30 mg/kg) cause an increase in extracellular glutamate in the NAc in drug naive rats [57, 62], but repeated cocaine injections or cocaine self-administration produces long-term depression in basal glutamate level in the mouse and rat NAc [47, 67]. Moreover drug craving and reinstatement (relapse) of cocaine-seeking behavior are supposed to be related to repeated cocaine-induced *reduction* in basal levels of glutamate transmission in the NAc during cocaine abstinence and to *enhanced* glutamate responses to acute cocaine priming [31, 55, 67, 72]. It should be noted that glutamate projection from the PFC to the NAc plays a critical role in cue-, stress- and cocaine-primed reinstatement of cocaine self-administration in animals after extinction [5, 16]. The problem of relapse to drug taking and drug-seeking behavior is a challenge for pharmacotherapy of drug addiction in human. The findings showed that systemic or local administration of AMN082 in the NAc, VP but not dorsal striatum (DS) inhibited cocaine-induced reinstatement of drug-seeking behavior in rats. AMN082 pre-treatment suppressed cocaine-induced increases in NAc glutamate. These two effects of AMN082 were blocked by intra-NAc microinjection of allosteric mGluR7 antagonist MMPIP and by systemic administration of the selective $mGluR_{2/3}$ antagonist LY3411495 [41]. As it was described previously, AMN082 alone increases extracellular glutamate in the NAc [39]. The elevated level of the NAc Glu activates the presynaptic mGluR2/3 on the PFC glutamatergic terminals. Next, the activation of mGluR2/3 counteracts cocaine-enhanced glutamate in the NAc. In results, pretreatment of AMN082 inhibits cocaine-induced reinstatement of drug-seeking behavior by mGluR2/3 mechanism [41].

THE MGLUR7 IN ALCOHOL DEPENDENCE

The critical role of glutamate in alcohol dependence is well known. Acute ethanol administration inhibits glutamatergic transmission by iGluRs (NMDA, AMPA) parti- cularly and also affects mGluRs. [12]. However, chronic alcohol exposure and abstinence induce glutamate system hyperactivity. It is suggested that chronic ethanol drinking causes reduction of number or activity of presynaptic II and III group mGluRs, which control excessive neurotransmitters release. In the consequence, glutamate system could be less controlled. This hypothesis is supported by genetic studies. Vadasz et al. [68] show that mGluR7-locus is *cis*-regulated gene for alcohol consumption. The mGluR7 knockout mice represented more consumption of ethanol in comparison to wild type littermates [25]. Moreover, there was evidence that the level of intermediary molecules, which are necessary for the production of mGluR7 proteins, were reduced in the hippocampus of the ethanol-dependent rats. Many findings emphasized mGluRs involvement in ethanol dependence i.e. mGluR2/3 agonist LY379268 as well as mGluR5 antagonist MPEP decreased ethanol self-administration in mice and alcohol preferring in rats [4, 7, 29, 38].

The most findings about the mGluR7 in alcohol dependence have been brought by studies of Bahi et al., who investigated the mGluR7 in alcohol reinforcement and rewarding processes. It was reported that allosteric agonist of mGluR7, AMN082 specifically reduced alcohol intake and preference in rats and mice in two-bottle free-choice paradigm without affecting taste preference, ethanol metabolism, and locomotor activity (at the doses used in inhibition of alcohol intake). Additionally, mGluR7 blockage with MMPIP enhanced alcohol consumption and preference in rats. The binge drinking was also suppressed by AMN082 in drinking in the dark (DID) model in mice [1, 2]. The author suggested at least three mechanisms that may explain these mGluR7 effects in ethanol preference and consumption. First, mGluR7 are associated with brain structures contributed to reinforcing effects of alcohol, such as the locus coeruleus, amygdala, or PFC. The second reason may derive from AMN082-induced increase of stress hormones. The mGluR7 plays a role in the glucocorticoid receptor-related negative feedback of the stress axis as well [48, 49]. Stress hormones have an influence on human drinking models [15, 20]. The mGluR7 activation in the hippocampus and/or hypothalamus may prevent excessive drinking of alcohol.

Finally, AMN082 decreases GABA release in the NAc causing an increase of the NAc Glu level. These changes could alter the occupancy of $GABA_B$ and NMDA receptors and counteract ethanol's allosteric modulating efficacy, resulting in reduced ethanol reward. Furthermore, the mGluR7 reduced ethanol-induced CPP without influence on locomotion. It confirms a role of the mGluR7 in brain reward [40].

The mGluR7 receptor is also regarded as modulator of ethanol sensitivity in mice [1]. AMN082 suppressed a few effects induced by acute ethanol exposure. This agent reduced sensitivity to ataxic effect of ethanol (assessed as the rotarod performance) and ethanol-induced locomotor activity. It is quite interesting that AMN082 decreased ethanol-induced acute withdrawal convulsions only when administered before alcohol injection, not after. That finding indicates that AMN082 inhibits some aspects of the development of ethanol dependence, but is not be able to counteract the expression acute withdrawal [1].

The mGluR7 has been investigated in the other aspect of alcohol addiction such as reinstatement to drug-seeking behavior after abstinence. It was reported that AMN082, administered after period of extinction, inhibited the reinstatement of ethanol-induced CPP and this effect was reverse by MMPIP, a selective allosteric antagonist of the mGluR7 [3]. It means that the mGluR7 takes part in memory related brain regions function: the PFC, NAc, amygdala, dorsal striatum, thalamus, hippocampus [33, 34]. AMN082 had no influence on ethanol-CPP extinction. However, in the other studies this agent facilitated extinction of conditioned fear [24]. It shows that the mGluR7 is not involved in modulation of negative learning in ethanol-extinction, but in ethanol conditioned reward memory. This result suggests that clinically activation of the mGluR7 in humans may promote alcohol abstinence and prevent relapse in the future. In addition, it is consistent with previous studies that revealed that AMN082 inhibited cocaine-induced reinstatement of drug-seeking behavior in rats [41]. The glutamatergic system seems to be a key of drug addiction and drug-related memory. The relapse to drug-taking behavior is linked to long-lasting drug effect such as neuroplasticity. Alcohol, similar to cocaine, produces neuroadaptive changes of glutamatergic transmission in the NAc, which lead to the development of drug-seeking behavior [45]. The mGluR7 may be able to maintain the normal balance of glutamatergic neurotransmission and modulate unnatural changes in neuronal excitability [12].

ADVANTAGE OF THE MGLUR7 OVER OTHER MGLURS

The mGluR7s become more sensitive during periods of intensive synaptic activity, for example after long-term drug exposure. These properties are different from other mGluRs, causing less adverse reactions [42]. Most findings showed that allosteric agonist of the mGluR7, AMN082 had no effect on the natural reward. This agent, administered alone, did not alter intracranial self-stimulation threshold [40], while the mGluR2/3 receptor agonist LY379268 and the mGluR5 receptor antagonist MPEP had aversive-like effect on eBSR [43]. Moreover, AMN082 did not interfere sweet (saccharin) fluid intake in rats, the natural reward for rodents [2]. The mGluR7 allosteric agonist did not change either basal or cocaine-enhance locomotor activity in the same doses that inhibited drug self-administration [2, 40]. Whereas mGluR2/3 agonist ***LY379268*** attenuated alcohol self-administration and reinstatement at doses that also decreased spontaneous locomotor activity [4]. Similarly, both EMQMCM mGluR1 antagonist and MTEP mGluR5 antagonist significantly reduced vertical motor activity [19]. The clash about influence of AMN082 on locomotor activity and natural reward is notable. In contrast to the above studies, Sailing et al. [58] revealed AMN082 reduced ethanol self-administration in mice, but it is nonspecific action because of inhibitory effect on general locomotor activity and natural reward (assessed in sucrose self-administration schedule). This data indicates a need for more research to explain these discrepancies, but generally, mGluR7 activation produces less adverse reaction than other mGluRs.

REFERENCES

1. Bahi A.: The pre-synaptic metabotropic glutamate receptor 7 "mGluR7" is a critical modulator of ethanol sensitivity in mice. *Neuroscience*, 199, 13, 2011.
2. Bahi A., Fizia K., Dietz M. et al.: Pharmacological modulation of mGluR7 with AMN082 and MMPIP exerts specific influences on alcohol consumption and preference in rats. *Addict. Biol.*, 17, 235, 2011.
3. Bahi A.: The selective metabotropic glutamate receptor 7 allosteric agonist AMN082 prevents reinstatement of extinguished ethanol-induced conditioned place preference in mice. *Pharmacol. Biochem. Behav.*, 101, 193, 2012.
4. Bäckstrom P., Hyytiä P.: Suppresion of alcohol self-administration and cue-induced reinstatement of alcohol seeking by the mGlu2/3 receptor agonist LY379268 and the mGlu8 receptor agonist (S)-3,4-DCPG. *Eur. J. Pharmacol.*, 528, 110, 2005.
5. Bäckstrom P., Hyytiä P.: Involvement of AMPA/kainite, NMDA, and mGlu5 receptors in the nucleus accumbens core in cue-induced reinstatement of cocaine seeking in rats. *Psychopharmacology*, 192, 571, 2007.
6. Benquet P., Gee C.E., Gerber U.: Two distinct signaling pathways upregulate NMDA receptor responces via two distinct metabotropic glutamate receptor subtypes. *J. Neurosci.,* 22, 9679, 2002.
7. Besheer J., Grondin J.J., Cannady R.: Metabotropic glutamate receptor 5 activity in the nucleus accumbens is required for the maintenance of ethanol self-administration in a rat genetic model of high alcohol intake. *Biol. Psychiatry*, 67, 812, 2010.
8. Bradley S.R., Rees H.D., Yi H. et al.: Distribution and developmental regulation of metabotropic glutamate receptor 7a in rat brain. *J. Neurochem.*, 71, 636, 1998.
9. Callaerts-Vegh Z., Beckers T., Ball S.M. et al.: Concomitant deficits in working memory and fear extinction are functionally dissociated from reduced anxiety in metabotropic glutamate receptor 7-deficient mice. *J. Neurosci*., 26, 6573, 2006.
10. Cartmell J., Schoepp D.D.: Regulation of neurotransmitter release by metabotropic glutamate receptors. *J. Neurochem.*, 75, 889, 2000.
11. Chen B. T., Bowers M. S., Martin M. et al.: Cocaine but not natural reward self-administration nor passive cocaine infusion produces persistent LTP in the VTA. *Neuron*., 59, 288, 2008.

12. Clapp P., Bhave S.V., Hoffman P.L.: How Adaptation of the Brain to Alcohol Leads to Dependence. *Alcohol Res. Health*, 31, 310, 2008.
13. Conn P.J., Pin J.P.: Pharmacology and functions of metabotropic glutamate receptors. *Annu. Rev. Pharmacol. Toxicol.*, 37, 205, 1997.
14. Conn P.J., Niswender C.M.: mGluR7's lucky number. *Proc. Natl. Acad. Sci. USA*, 103, 251, 2006.
15. Cooper M.L., Russell M., Skinner J.B. et al.: Stress and alcohol use: moderating effects of gender, coping, and alcohol expectancies. *J. Abnorm. Psychol.*, 101, 139, 1992.
16. Cornish J.L., Kalivas P.W.: Glutamate transmission in the nucleus accumbens mediates relapse in cocaine addiction. *J. Neurosci*., 20, RC89, 2000.
17. Cryan J.F., Kelly P.H., Neijt H.C. et al.: Antidepressant and anxiolytic-like effects in mice lacking the group III metabotropic glutamate receptor mGluR7. *Eur. J. Neurosci.*, 17, 2409, 2003.
18. Dewey S.L, Morgan A.E, Ashby C.R. Jr et al.: A novel strategy for the treatment of cocaine addiction. *Synapse*, 30, 119, 1998.
19. Dravolina O.A., Danysz W., Bespalov A.Y.: Effects of group I metabotropic glutamate receptor antagonists on the behavioral sensitization to motor effects of cocaine in rats. *Psychopharmacology*, 187, 397, 2006.
20. Fahlke C., Engel J.A., Eriksson C.J. et al.: Involvement of corticosterone in the modulation of ethanol consumption in the rat. *Alcohol.*, 11, 195, 1994.
21. Fendt M., Schmid S., Thakker D.R. et al.: mGluR7 facilitates extinction of aversive memories and controls amygdale plasticity. *Mol. Psychiatry*, 13, 970, 2008.
22. Ferraguti F., Shigemoto R.: Metabotropic glutamate receptors. *Cell. Tissue. Res.*, 326, 483, 2006.
23. Gereau R.Wt., Conn P.J.: Multiple presynaptic metabotropic glutamate receptors excitatory and inhibitory synaptic transmission in hippocampal area CA1. *J. Neurosci.*, 15, 6879, 1995.
24. Groblewski P.A., Lattal K.M., Cunningham C.L.: Effects of D-cycloserine on extinction and reconditioning of ethanol-seeking behavior in mice. *Alcohol Clin. Exp. Res.*, 33, 772, 2009.
25. Gyetvai B., Simonyi A., Oros M. et al.: MGluR7 genetics and alcohol: intersection yields clues for addiction. *Neurochem. Res.*, 36,1087, 2011.
26. Haile C. N., Mahoney J. J. III, Newton T. F. et al.: Pharmacotherapeutics directed at deficiencies associated with cocaine dependence: Focus on dopamine, norepinephrine and glutamate. *Pharmacol. Therapeut.*, 134, 260, 2012.
27. Harris G.C., Aston-Jones G.: Critical role for ventral tegmental glutamate in preference for a cocaine-conditioned environment. *Neuropsychopharmacology,* 28, 73, 2003.
28. Hikichi H., Murai T., Okuda S. et al.: Effects of a novel metabotropic glutamate receptor 7 negative allosteric modulator, 6-(4-methoxyphenyl)-5-methyl-3-pyridin-4-ylisoxazonolo[4,5-c]pyridin-4(5H)-one (MMPIP), on the central nervous system in rodents. *Eur. J. Pharmacol.*, 639, 106, 2010.
29. Hodge C.W., Miles M.F., Sharko A.C. et al.: The mGluR5 antagonist MPEP selectively inhibits the onset and maintenance of ethanol self-administration in C57BL/6J mice. *Psychopharmacology*, 183, 429, 2010.
30. Kalivas P.W., Duffy P.: Repeated cocaine administration alters extracellular glutamate in the ventral tegmental area. *J. Neurochem.*, 70, 1497, 1998.
31. Kalivas P.W.: Glutamate systems in cocaine addiction. *Curr. Opin. Pharmacol.*, 4, 23, 2004.
32. Kalivas P.W., O'Brien C.: Drug addiction as a pathology of staged neuroplasticity. *Neuropsychopharmacology,* 33, 166, 2008.
33. Kinoshita A., Shigemoto R., Ohishi H. et al.: Immunohistochemical localization of metabotropic glutamate receptors, mGluR7a and mGluR7b, in the central nervous system of the adult rat and mouse: a light and electron microscopic study. *J. Comp. Neurol.,* 393, 332, 1998.
34. Kinzie J.M., Saugstad J.A., Westbrook G.L. et al.: Distribution of metabotropic glutamate receptor 7 messenger RNA in the developing and adult rat brain. *Neuroscience,* 69, 167, 1995.
35. Knackstedt L.A., Moussawi K., Lalumiere R. et al.: Extinction training after cocaine self-administration induces glutamatergic plasticity to inhibit cocaine seeking. *J. Neurosci.*, 30, 7984, 2010.
36. Koob G.F., Bloom F.E.: Cellular and molecular mechanisms of drug dependence. *Science,* 242, 715, 1988.
37. Kotlińska J., Bocheński M.: Comparison of the effects of mGluR1 and mGluR5 antagonists on the expression of behavioral sensitization to the locomotor effect of morphine and Eur. *J. Pharmacol.*, 558, 113, 2007.
38. Kotlińska J., Bocheński M., Danysz W.: The role of group I mGlu receptors in the expression of ethanol-induced conditioned place preference and ethanol withdrawal seizures in rats. *Eur. J. Pharmacol.*, 670, 154, 2011.
39. Li X., Gardner E. L, Xi Z. X.: The metabotropic glutamate receptor 7 (mGluR7) allosteric agonist AMN082 modulates nucleus accumbens GABA and glutamate, but not dopamine, in rats. *Neuropharmacology*, 54, 542, 2008.
40. Li X., Li J., Peng X. Q. et al.: Metabotropic glutamate receptor 7 modulates the rewarding effects of cocaine in rats: involvement of a ventral pallidal GABAergic mechanism. *Neuropsychopharmacol.*, 34, 1783, 2009.
41. Li X., Li J., Gardner E. L. et al.: Activation of mGluR7s inhibits cocaine-induced reinstatement of drug-seeking behavior by a nucleus accumbens glutamate-mGluR2/3 mechanism in rats. *J. Neurochem.*, 114, 1368, 2010.
42. Li X., Xi Z. X., Markou A.: Metabotropic glutamate 7 (mGlu7) receptor: A target for medication development for the treatment of cocaine dependence. *Neuropharmacology*, in press, 2012.
43. Liechti M.E., Markou A.: Metabotropic glutamate 2/3 receptors activation induced reward deficits but did not aggravate brain reward deficits associated with spontaneous nicotine withdrawal in rats. *Biochem. Pharmacol.*,74, 1299, 2007.
44. Marino M.J., Conn P.J.: Glutamate-based therapeutic approaches: allosteric modulators of metabotropic glutamate receptors. *Curr. Opin. Pharmacol.*, 6, 98, 2006.
45. Marty V.N., Spigelman I.: Long-lasting alterations in membrane properties, K+ currents, and glutamatergic synaptic currents of nucleus accumbens medium spiny neurons in a rat model of alcohol dependence. *Front. Neurosci*., 6, 86, 2012.
46. Masugi M., Yokoi M., Shigemoto R. et al.: Metabotropic glutamate receptor subtype 7 ablation causes deficit in fear response and conditioned taste aversion. *J. Neurosci.*, 19, 955, 1999.
47. Miguéns M., Del Olmo N., Higuera-Matas A. et al.: Glutamate and aspartate levels in the nucleus accumbens during cocaine self-administration and extinction: a time course microdialysis study. *Psychopharmacology*, 196, 303, 2008.
48. Mitsukawa K., Yamamoto R., Ofner S. et al.: A selective metabotropic glutamate receptor 7 agonist: activation of receptor signaling via an allosteric site modulates stress parameters in vivo. *P. Natl. Acad. Sci. USA*, 102, 18712, 2005.
49. Mitsukawa K., Mombereau C., Lotscher E. et al.: Metabotropic glutamate receptor subtype 7 ablation causes dysregulation of the HPA axis and increases hippocampal BDNF protein levels: implications for stress-related psychiatric disorders. Neuropsychopharmacology, 31, 1112, 2006.
50. Moussawi K., Kalivas P.W.: Group II metabotropic glutamate receptors (mGluR2/3) in drug addiction. *Eur. J. Pharmacol.*, 639, 115, 2010.
51. Niswender C. M., Conn P. J.: Metabotropic glutamate receptors: physiology, pharmacology, and disease. *Annu. Rev. Pharmacol.*, 50, 295, 2010.

52. O'Connor R. M., Finger B. C., Flor P. J. et al.: Metabotropic glutamate receptor 7: at the interface of cognition and emotion. *Eur. J. Pharmacol.*, 10, 123, 2010.
53. Olive M.F.: Metabotropic glutamate receptor ligands as potential therapeutics for addiction. *Curr. Drug Abuse Rev.*, 2, 83, 2009.
54. Palucha A., Klak K., Branski P. et al.: Activation of the mGlu7 receptor elicits antidepressant-like effects in mice. *Psychopharmacology*, 194, 555, 2007.
55. Pierce R.C., Bell K., Duffy P. et al.: Repeated cocaine augments excitatory amino acid transmission in the nucleus accumbens only in rats having developed behavioral sensitization. *J. Neurosci.*, 16, 1550, 1996.
56. Pin J.P., Duvoisin R.: The metabotropic glutamate receptors: structures and functions. *Neuropharmacology*, 34, 1, 1995.
57. Reid M.S., Hsu K. Jr, Berger S.P.: Cocaine and amphetamine preferentially stimulate glutamate release in the limbic system: studies on the involvement of dopamine. *Synapse*, 27, 95, 1997.
58. Salling M.C., Faccidomo S., Hodge C.W.: Nonselective suppression of operant ethanol and sucrose self-administration by the mGluR7 positive allosteric modulator AMN082. *Pharmacol. Biochem. Be.*, 91, 14, 2008.
59. Self D.W., Nestler E.J.: Molecular mechanisms of drug reinforcement and addiction. *Annu. Rev. Neurosci.*, 18, 463, 1995.
60. Shen H-wei, Toda S., Moussawi K. et al.: Altered dendritic spine plasticity in cocaine-withdrawn rats. *J. Neurosci.*, 29, 2876, 2009.
61. Siegl S., Flor P.J., Fendt M.: Amygdaloid metabotropic glutamate receptors subtype 7 is involved in the acquisition of conditioned fear. *Neuroreport,* 19, 1147, 2008.
62. Smith J.A., Mo Q., Guo H. et al.: Cocaine increases extraneuronal levels of aspartate and glutamate in the nucleus accumbens. *Brain Res.*, 683, 264, 1995.
63. Stachowicz K., Branski P., Klak K. et al.: Selective activation of metabotropic G-protein-coupled glutamate 7 receptor elicits anxiolytic-like effects in mive by modulating GABAergic transmission. *Behav. Pharmacol.*, 19, 597, 2008.
64. Sun H., Ma C.L., Kelly J.B. et al.: $GABA_B$ receptor-mediated presynaptic inhibition of glutamatergic transmission in the inferior colliculus. *Neurosci. Lett.*, 399, 151, 2006.
65. Sukoff Rizzo SJ, Leonard SK, Gilbert A. et al.: The metabotropic glutamate receptor 7 allosteric modulator AMN082: a monoaminergic agent in disguise? *J. Pharmacol. Exp. Ther.*, 338, 345, 2011.
66. Suzuki G., Tsukamoto N., Fushiki H. et al.: In vitro pharmacological characterization of novel isoxazolopyridone derivatives as allosteric metabotropic glutamate receptor 7 antagonists. *J. Pharmacol. Exp. Ther.*, 323, 147, 2007.
67. Thomas M.J., Beurrier C., Bonci A. et al.: Long-term depression in the nucleus accumbens: a neural correlate of behavioral sensitization to cocaine. *Nat Neurosci.*, 4, 1217, 2001.
68. Vadasz C., Saito M., Gyetvai B. et al.: Glutamate receptor metabotropic 7 is cis-regulated in the mouse brain and modulates alcohol drinking. *Genomics*, 90, 690, 2007.
69. Wise R.A., Gardner E.L.: *Animal models of addiction*. In: Charney D.S., Nestler E.J. (eds). Neurobiology of Mental illness 2nd edn. Oxford Univ. Press: London. 10-20, 2004.
70. Wise R.A.: Forebrain substrates of reward and motivation. *J. Comp. Neurol.,* 493, 115, 2005.
71. Wolf M.E., Xue C.J., Li Y. et al.: Amphetamine increases glutamate efflux in the rat ventral tegmental area by a mechanism involving glutamate transporters and reactive oxygen species. *J. Neurochem.*, 75, 1634, 2000.
72. Xi Z-X., Stein E.A.: GABAergic mechanisms of opiate reinforcement. *Alcohol.*, 37, 485, 2002.
73. Xi Z-X., Ramamoorthy S., Shen H. et al.: GABA transmission in the nucleus accumbens is altered after withdrawal from repeated cocaine. *J. Neurosci.*, 23, 3498, 2003.