

Metabotropic Glutamate Receptor 7: From Synaptic Function to Therapeutic Implications

Enza Palazzo^{1,2,*}, Ida Marabese², Vito de Novellis², Francesco Rossi² and Sabatino Maione²

¹Department of Anesthesiology, Surgery and Emergency, The Second University of Naples, Piazza Luigi Miraglia 2, 80138 Naples, Italy; ²Department of Experimental Medicine, Pharmacology Division "L. Donatelli", The Second University of Naples, via Costantinopoli 16, 80138 Naples, Italy



Enza Palazzo

Abstract: Metabotropic glutamate receptor 7 (mGluR7) is localized presynaptically at the active zone of neurotransmitter release. Unlike mGluR4 and mGluR8, which share mGluR7's presynaptic location, mGluR7 shows low affinity for glutamate and is activated only by high glutamate concentrations. Its wide distribution in the central nervous system (CNS) and evolutionary conservation across species suggest that mGluR7 plays a primary role in controlling excitatory synapse function. High mGluR7 expression has been observed in several brain regions that are critical for CNS functioning and are involved in neurological and psychiatric disorder development. Until the recent discovery of selective ligands for mGluR7, techniques to elucidate its role in neural function were limited to the use of knockout mice and gene silencing. Studies using these two techniques have revealed that mGluR7 modulates emotionality, stress and fear responses. N,N'-dibenzhydrylethane-1,2-diamine dihydrochloride (AMN082) was reported as the first selective mGluR7 allosteric agonist. Pharmacological effects of AMN082 have not completely confirmed the mGluR7-knockout mouse phenotype; this has been attributed to rapid receptor internalization after drug treatment and to the drug's apparent lack of *in vivo* selectivity. Therefore, the more recently developed mGluR7 negative allosteric modulators (NAMs) are crucial for understanding mGluR7 function and for exploiting its potential as a target for therapeutic interventions. This review presents the main findings regarding mGluR7's effect on modulation of synaptic function and its role in normal CNS function and in models of neurologic and psychiatric disorders.

Keywords: Affective and cognitive behavior, mGluR7 knockout mice phenotype, mGluR7, pain, selective mGluR7 allosteric modulators, stress response.

Received: February 13, 2015

Revised: May 20, 2015

Accepted: July 14, 2015

INTRODUCTION

The actions of glutamate, the main excitatory neurotransmitter in the mammalian central nervous system (CNS), can be finely modulated by metabotropic glutamate receptors (mGluRs) [1, 2]. mGluRs are G-protein coupled receptors and are divided into three groups based on sequence homology, pharmacological profile, and signal transduction mechanisms [3]. Eight mGluRs (mGluR1-8) have been identified and classified into three groups: group I, consisting of mGluR1 and mGluR5, group II, consisting of mGluR2 and mGluR3, and group III, consisting of mGluR4, mGluR6, mGluR7, and mGluR8. Group I receptors are coupled to phospholipase C (PLC) activation, while Group II and III are associated with adenylate cyclase inhibition [3, 4]. mGluRs modulate glutamatergic transmission at several levels depending on their expression at nerve terminals, postsynaptic sites, or glia [5, 6] (Fig. 1). Group I mGluRs are mainly located at the postsynaptic regions, where they increase neural excitability, whereas group II and group III are primarily located at presynaptic terminals and

function as inhibitory auto- and hetero-receptors [7, 8]. While mGluR6 is exclusively expressed in the retina [9], the other mGluRs are widely distributed throughout the nervous system. Group III is the largest group of mGluRs and the least well-characterized, likely due to the lack of selective pharmacologic agents. Selective allosteric ligands for group III mGluR subtypes were recently discovered; this has made it possible to elucidate the role of each of these receptors in normal CNS functioning and in models of neurologic and psychiatric disorders. Recently, a brain penetrant preferential agonist for mGluR4, (2S)-2-amino-4-(hydroxy(hydroxy(4-hydroxy-3-methoxy-5-nitrophenyl)methyl)phosphoryl)butanoic acid (LSP1-2111) was identified. Preclinical studies suggest that LSP1-2111 has *in vivo* efficacy in models of Parkinson's disease, anxiety, psychosis, fear learning, and memory [10]. These studies rationalize further investigations on the therapeutic benefits of mGluR modulators that can finely tune glutamatergic transmission in an effort to treat various psychiatric and neurologic conditions.

EXPRESSION PATTERNS OF mGluR7

Out of the group III mGluRs, mGluR7 is the most widely expressed throughout the CNS [7, 11, 12]. The highest density of mGluR7 expression is in the olfactory bulb, hippocampus, hypothalamus, and sensory afferent pathways

*Address correspondence to this author at the Department of Anesthesiology, Surgery and Emergency, The Second University of Naples, Piazza Luigi Miraglia 2, 80138 Naples, Italy; Tel: +39-(0)81-5665880; Fax: +39-(0)81-5667503; E-mail: enza.palazzo@unina2.it

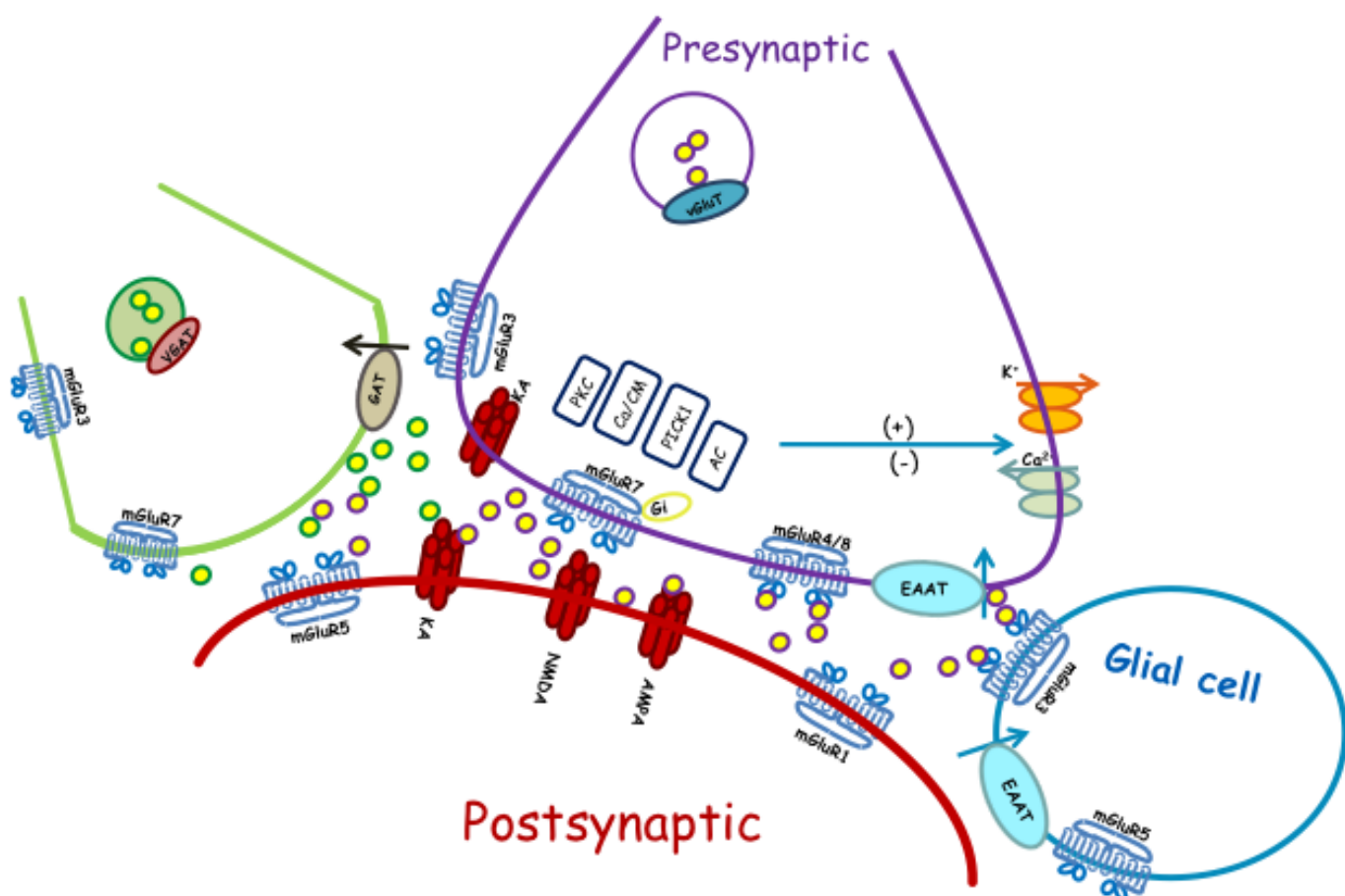


Fig. (1). Synaptic distribution of mGluRs with group I localized mainly postsynaptically and group II and III localized presynaptically. The mGluR7 receptor is found on both glutamatergic and GABAergic terminals, functioning as an auto- and hetero-receptor and controlling neurotransmitter release. Together with excitatory amino acid transporters (EAAT), presynaptic mGluR7 receptors reduce glutamate levels under conditions of high glutamate concentration. mGluR7 binding and signaling proteins are also reported. VGAT, vesicular GABA transporter; vGluT, vesicular glutamate transporter; EAAT, excitatory amino acid transporter; NMDA, N-methyl-D-aspartate receptor; AMPA, α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor, KA, kainic acid receptor, CaM, Ca²⁺-calmodulin complex, PKC, protein kinase C, AC, adenylate cyclase, PICK1, PDZ domain-containing protein, Ca²⁺, N type Ca²⁺ channels, GIRKs, G-protein-coupled inwardly rectifying potassium channels.

[11, 13-15]. mGluR7 receptors are mainly located within the presynaptic active zone [11, 14, 16] where they serve as auto- or hetero-receptors, inhibiting glutamate or GABA release, respectively [16, 17] (Fig. 1). mGluR7 receptor activation also leads to increased signaling pathways potentiating neurotransmitter release in cerebrocortical nerve terminal preparations from adult rats [18]. However, direct facilitation of neurotransmitter release by mGluR7 has not yet been demonstrated on neurons *in vitro* or *in vivo*. In the globus pallidus and striatum, mGluR7 is expressed at postsynaptic sites and not just at presynaptic ones [19]. Postsynaptic mGluR7 receptors have also been observed on amacrine cells at retinal synapses [20], on olfactory bulb glomeruli [21], and on prefrontal cortex pyramidal neurons [22]. So far, five splice variants of the mGluR7 receptor have been characterized, called mGluR7a-e. These splice variants exhibit different, but often overlapping, expression patterns [12, 23-25]. mGluR7a is generally more widely expressed than mGluR7b [14, 24]. mGluR7c and mGluR7d are found in non-neuronal tissues within the CNS [25]. In addition to

its CNS localization, mGluR7 is also expressed in peripheral tissues, such as the colon [26], stomach [27], and adrenal glands [28], and in hair cells and spiral ganglion cells of the inner ear [29].

ROLE OF mGluR7 IN SYNAPTIC TRANSMISSION

mGluR7 has low affinity for glutamate; it is recruited only under high neurotransmitter concentrations and thus acts as an auto-receptor to inhibit further glutamate release [30]. L-2-amino-4-phosphonobutyrate (L-AP4) can bind to mGluR7 at high concentrations and inhibits glutamate release *via* N-type Ca²⁺ channel inhibition [31] (Fig. 1). Recently, studies using the selective mGluR7 positive allosteric agonist N,N'-bis(diphenylmethyl)-1,2-ethanediamine dihydrochloride (AMN082) and the mGluR7 negative allosteric modulator 7-hydroxy-3-(4-iodophenoxy)-4H-chromen-4-one (XAP044) have demonstrated that mGluR7 modulates excitatory/inhibitory transmission in the hippocampus [32-35], thalamus [36,37], nucleus accumbens [38, 39], PAG [40] and amygdala [41-43]. Effects of AMN082

differ depending on the brain region. Specifically, AMN082 decreases GABA and increases glutamate levels in the nucleus accumbens [39] and amygdala [42]. Conversely, it decreases glutamate release in the PAG [40]. In some instances, mGluR7 facilitates glutamatergic release, likely *via* interactions with the exocytose machinery [18]. Apart from Gi/o-protein coupling and the consequent inhibition of adenylyl cyclase and cAMP formation [1], mGluR7 also inhibits N- and P/Q-type Ca²⁺ channels in the transfected cerebellar granule cells [44], brainstem [45], and hippocampus [46, 47]. Finally, mGluR7 also modulate synaptic function through G-protein-coupled inwardly rectifying potassium channels (GIRKs) [48].

mGluR7 activity is finely modulated: calmodulin binds to the carboxyl terminus of mGluR7 in a Ca²⁺-dependent manner (CaM). The CaM-binding domain, located at the end of the seventh trans-membrane segment, can be competitively phosphorylated by protein kinase C (PKC), which inhibits binding of the Ca²⁺/CaM complex to the receptor [49]. PKC inhibits mGluR7's effect on neurotransmitter release by preventing coupling of mGluR7 receptors to their requisite G proteins [50]. PKC-mediated phosphorylation is also a key mechanism regulating constitutive and activity-dependent mGluR7 expression. Two events, mGluR7 phosphorylation by PKC and mGluR7 binding to the PDZ domain-containing protein PICK1, lead to increased mGluR7 expression [51]. mGluR7 expression is also increased by inhibitors of protein phosphatase 1 (PP1), which counteracts the action of PKC on mGluR7 [52]. Rodent studies suggest that the interaction of mGluR7 and PICK1 is critical to proper neural function, as disruption of the mGluR7a-PICK1 complex is sufficient to induce absence epilepsy-like seizures [53]. It has also been suggested that mGluR7 activity is protective against several neurological disorders. mGluR7 modulates GABAergic interneuron synapse development through its interaction with Elfn1 protein, whose abnormal expression during development is associated with epilepsy and attention deficit hyperactivity disorders [54]. mGluR7 also prevents NMDA-induced excitotoxicity of basal forebrain (BF) cholinergic neurons; degeneration of these neurons represents an early pathological event in Alzheimer's disease. This protection mechanism through mGluR7 activation is selectively inhibited by β -amyloid (A β). A β increases p21-activated kinase activity and decreases cofilin-mediated actin depolymerization through a p75(NTR)-dependent mechanism [55].

EXAMINATION OF THE mGluR7 KNOCK-OUT PHENOTYPE

Due to the lack of available ligands with specificity for mGluR7, mGluR7-knockout mice were traditionally the only tool available to examine the physiological role of mGluR7 and its involvement in cognitive, affective, and sensory behaviors [56]. Mice lacking mGluR7 receptors showed reduced short-term neural plasticity in the hippocampus [57] suggesting a role for mGluR7 in the molecular mechanisms underlying cognition. In line with this evidence, mGluR7-knockout mice displayed some impairments in learning and memory [58-60]. Specifically, these mice showed normal behavior in the T-maze [58] but impairments in both the 4-arm and 8-arm maze tasks, which require intact working

memory capacity. Intriguingly, after training, mGluR7-knockout mice showed test performance similar to their wild type counterparts, implying that training can overcome baseline differences in working memory capacity [58, 59, 61]. Similarly, mGluR7-deficient mice exhibited impairments in the Morris water maze, although they achieved similar performance to wild type mice after training [62]. It has been thus proposed that mGluR7 is involved in the molecular mechanisms underlying short-term working and spatial memory whereas long-term memory operates in an mGluR7-independent manner [58, 62]. Recent studies have also demonstrated that mGluR7 is involved in conditioned fear responses. Mice lacking mGluR7 displayed delayed extinction of a conditioned fear response in the conditioned emotional responses (CER) procedure, but the initial acquisition of fear responses appeared unaltered in these mice [62, 63]. This may be due to the different neural substrates involved in acquisition (the amygdala) and extinction (the hippocampus and prefrontal cortex) of CER. However, mGluR7-deficient mice displayed reduced shock-induced freezing and impaired conditioned taste aversion, which are both amygdala-dependent paradigms [64-66]. The reason for these discrepant findings may be the different experimental strategies used in the two studies. The CER study used shocks that were signaled by auditory cues [62], and the conditioned taste aversion study used saccharin avoidance after pairing it with intraperitoneal injection of LiCl, an agent which causes transient visceral malaise [66]. mGluR7-knockout mice exhibited reduced anxiety-like responses in several behavioral tests such as the elevated plus maze, staircase, marble burying, light-dark box, open field, and stress-induced hyperthermia tests [62,67]. The behavioral profile of these mice suggests a role for mGluR7 in emotional disorders [68]. In addition, and in accordance with their anxiolytic-like phenotype, mGluR7 knockout mice also displayed reduced stress responses and activity of the hypothalamic-pituitary-adrenal (HPA) axis [70]. mGluR7-deficient mice showed increased expression of hippocampal glucocorticoid and 5-hydroxytryptamine 1A receptors (GR and 5-HT_{1A}) [70]. Increased GR and 5-HT_{1A} expression in response to the lack of mGluR7 suggests enhanced negative feedback of the HPA axis, which is hyperactive in depressant and anxiety-like phenotypes [71, 72]. Accordingly, mGluR7-knockout mice showed increased HPA suppression in response to dexamethasone and increased levels of brain derived neurotrophic factor (BDNF), both positive indexes of antidepressant activity [73, 74]. Consistently, mGluR7-knockout mice exhibited antidepressant-like profiles in the tail suspension and forced swim tests [67, 75]. Mice lacking the mGluR7 receptor displayed an increased seizure vulnerability and reduced anticonvulsant effects of (RS) phosphonophenylglycine (PPG), a broad spectrum group III mGluR agonist [56], indicating a potential neuroprotective role for mGluR7 [76]. The phenotype of the mGluR7 knockout mouse is summarized in Table 1. Altogether, mGluR7-knockout mouse strategies have largely contributed to uncovering the role of mGluR7 in epilepsy, cognition, and emotion regulation. One critical limitation of conventional knockout strategies, however, is that the constitutive lack of a gene may lead to compensatory effects from related proteins, especially during development, and this may

Table 1. A summary of the effects of selective mGluR7 ligands and the behavioral phenotype of mGluR7-knockout mice. The experimental *in vitro* and *in vivo* model used, along with related references, are also indicated.

Experimental Strategies	Outcomes	Test	Refs.
Synaptic function			
AMN082	Inhibition of excitatory transmission in the hippocampus	LTD	[34]
AMN082	Lowered extracellular GABA and increased extracellular glutamate in the nucleus accumbens	<i>In vivo</i> brain microdialysis	[38]
AMN082	Decreased glutamate and GABA release in the PAG, decreased tail flick latency, increased the pause and shortened the onset of the pause of the OFF cells in the RVM	<i>In vivo</i> microdialysis, <i>In vivo</i> electrophysiological recordings	[40]
AMN082	Inhibition of synaptic transmission in the amygdala	fEPSPs evoked by stimulation at low frequency, Patch-clamp	[41,42]
mGluR7 knockout mice phenotype			
	Reduced short term plasticity in the hippocampus	LTP	[57]
	Reduced short-term working memory	4-arm and 8-arm maze task	[58]
	Altered theta activity (6-12 Hz) in EEGs	EEGs	[59]
	Impairments in acquisition and extinction	Appetitive odor conditioning, Scheduled appetitive conditioning, Conditioned emotional response, Discriminated conditioned emotional response, Contextual fear conditioning	[61]
	Impairments in spatial memory	Morris water maze	[62]
	Impairments to extinction of fear-elicited response	Pavlovian fear conditioning	
	Anxiolytic-like behavior	Light-dark box, Elevated plus maze, Staircase test, Stress-induced hyperthermia	[67]
	Antidepressant-like behavior	Forced swim test, Tail suspension test, BDNF levels	[67,70]
	Reduced amygdala-dependent fear learning	Freezing after electric shock, Conditioned taste aversion	[66]
	Dysregulation of HPA axis parameters	ACTH and corticosterone levels, Dexamethasone-induced suppression of serum corticosterone, GR and 5-HT _{1A} mRNA transcripts	[70,73]
	Increased seizure susceptibility	Increased seizure vulnerability and reduced anticonvulsant effect to (RS) phosphophenylglycine, PPG	[56]
Pharmacology			
AMN082	Increased HPA activity	Increased corticosterone and ACTH plasma levels	[78]
AMN082	Reduced fear acquisition and LTP in the amygdala and improved fear extinction	Fear-potentiated startle, Conditioned taste aversion	[85]
AMN082	Blocked conditioned fear learning	Measurement freezing duration	[69]
AMN082	Anxiety-like behavior	Elevated plus maze	[88]
AMN082	Anxiolytic-like effect	Stress induced hyperthermia and four plate test	[68]
AMN082	Antidepressant-like effect	Forced swim test, Tail suspension test	[89,91,92, 97]
AMN082	Facilitated nociception	Tail flick test, Mechanical withdrawal threshold, Capsaicin-induced cardiac-somatic reflex, Hot plate test	[40,88,93,97]
AMN082	Decreased nociception	Formalin test, Mechanical allodynia	[98,99]
AMN082	Reduced ethanol and cocaine intake	Ethanol preference drinking, Intracranial self-stimulation procedure, Cocaine- or cue-induced reinstatement of drug-seeking behavior	[101,102]
MMPIP	Impaired cognitive performance and reduced social interaction in healthy rodents	Object recognition, Radial arm maze, Social interaction test	[105]
MMPIP	Decreased nociception in formalin and neuropathic pain conditions, increased the activity of the OFF cells and decreased those of the ON cells in the RVM	Formalin test, Tail flick, Single Unit electrophysiological recordings	[106]
ADX71743	Anxiolytic-like and antipsychotic-like effect	ADX71743 Anxiolytic-like and antipsychotic-like effect Marble burying, Elevated plus maze, Amphetamine-induced hyperactivity	[109]
XAP044	Anxiolytic like-effect	Elevated plus maze, Stress induced hyperthermia, Fear conditioning paradigm	[43]
XAP044	Antidepressant like effect	Tail suspension	[43]

confound some outcome measures. To address this concern, the development of selective mGluR7 ligands for direct activation/blockade of the receptor in the adult organism is critical.

PHARMACOLOGICAL MANIPULATION OF mGluR7

mGluR7 displays low affinity for the “classic” group III orthosteric agonists such as L-AP4 and L-SOP [77]. Moreover, orthosteric receptor activation requires an α -amino acid moiety and distal phosphonic group, which makes these compounds too hydrophilic to penetrate the blood-brain-barrier for subsequent brain exposure [78]. ACPT-1 can penetrate the blood-brain-barrier, but has shown the same low selectivity for mGluR7 [79, 80]. The competitive group III mGluR antagonist, LY341495, shows the highest potency but is scarcely selective, since it is also a potent antagonist at group II mGluRs [81]. MSOP, CPPG, and MAP4 are more selective for group III mGluRs but display weak potency [30, 77]. Targeting allosteric binding sites has permitted drug developers to overcome the scarce selectivity and hydrophilicity associated with orthosteric compounds. Allosteric binding sites are less conserved among the other mGluR family members and do not require hydrophilic moieties [82]. AMN082 was developed as the first selective positive allosteric modulator (PAM) for mGluR7 [78]. The interest in AMN082 has waned because of its scarce selectivity *in vivo* [83]. AMN082 fully activates mGluR7 [78, 84], and its action is not blocked by mGluR7 orthosteric antagonists [78]. AMN082, however, is rapidly metabolized into an active compound *in vivo*, which inhibits monoamine transporter activity. Consistent with the mGluR7-knockout mouse phenotype, AMN082 increases plasma corticosterone and adrenocorticotropic hormone (ACTH) levels [78]. AMN082 has been shown to reduce fear acquisition and LTP in the amygdala, but improve fear extinction [85,86]. AMN082's effect on fear extinction is in line with the resistance to fear extinction observed in mGluR7-deficient mice, whereas its effect on fear acquisition is divergent from the phenotype of mGluR7-deficient mice, which displayed no abnormality in fear acquisition [62]. AMN082's effects on emotional behavior also conflict those of mGluR7-knockout phenotype. AMN082 paradoxically produced anxiogenic-and anxiolytic-like effects [68, 69, 85, 88-90] and also demonstrated antidepressant-like activity [89, 91, 92], the latter being in contrast to the mGluR7-knockout phenotype. AMN082 also facilitated nociception when microinjected into the ventrolateral PAG (VL PAG), central nucleus of the amygdala (CeA), or nucleus tractus solitarius (NTS) [40, 88, 93]. AMN082 changed the activity of neurons that respond to pain stimuli in the rostral ventromedial medulla (RVM) and decreased glutamate release into the VL PAG [40], consistently with descending pathway inhibition and pain facilitation [40, 94-96]. AMN082 has been shown to facilitate nociception in some studies [97]; however, it reduced pain responses in other studies [98, 99]. One possible explanation for the contradictory effects of AMN082 is the rapid and long-lasting mGluR7 receptor internalization induced by AMN082, which coincides with functional

antagonism. Alternatively, AMN082's scarce selectivity for mGluR7 *in vivo* suggests the possibility of off-target involvement [83, 100]. AMN082 also reduces ethanol and cocaine intake [101, 102], facilitates the extinction of aversive memories [85], and increases colonic secretory function [26]. The recent discovery of novel negative allosteric modulators (NAMs) for mGluR7 will likely contribute to better understanding of the functional role for mGluR7 in neural functioning. 6-(4-methoxyphenyl)-5-methyl-3-pyridin-4-ylisoxazolo[4,5-c]pyridin-4(5H)-one (MMPIP), a selective negative allosteric modulator for mGluR7, has shown inverse agonist activity for mGluR7 and good brain exposure after systemic administration [103, 104]. *In vivo* studies with MMPIP have shown that negative allosteric modulation of mGluR7 impairs cognitive performance in the object recognition and radial arm maze tasks and reduces social interaction in rodents. MMPIP has been found to be ineffective in a range of behavioral experiments aimed at investigating motor coordination, anxiety and depression-like behaviors, sensorimotor gating, seizure threshold, and nociception in healthy rodents [105]. Later, a recent paper from our laboratory confirmed that, when administered into the VL PAG, MMPIP showed no effect in healthy rats but inhibited pain responses in formalin and neuropathic pain models. MMPIP altered pain thresholds by modulating the antinociceptive descending pathway at RVM levels when administered into the VL PAG. Specifically, in neuropathic rats it increased the activity of antinociceptive OFF cells and decreased that of pronociceptive ON cells, consistently with antinociception, but proved ineffective in healthy controls [106]. This context-dependent MMPIP effect was confirmed in a novel study where MMPIP was shown to reverse the main symptoms of neuropathic pain in the spared nerve injury model, while remaining ineffective in control mice. In neuropathic mice, systemic MMPIP administration increased thermal and mechanical thresholds, occurrence of open-arm choice in the elevated plus maze, reduced immobility in the tail suspension test, and reduced the number of marbles buried and digging events in the marble-burying test, thus demonstrating putative anxiolytic- and antidepressant-like properties. MMPIP also improved cognitive performance, which is deeply compromised in neuropathic mice. It appears that for mGluR7 blockade to be effective, some neuroplasticity is required. Changes in receptor expression in some supraspinal areas such as the basolateral amygdala, dorsal raphe, prelimbic cortex, PAG, and hippocampus have been observed in neuropathic conditions. This may enhance MMPIP's effect [107]. In line with the efficacy of MMPIP in chronic pain models and its lack of effect in healthy animals, MMPIP showed context-dependent activity in recombinant cell lines and inactivity under normal physiological conditions [108]. Other selective mGluR7 NAMs have recently been developed: 7-hydroxy-3-(4-iodophenoxy)-4H-chromen-4-one (XAP044), which has shown to inhibit long-term potentiation (LTP) in the lateral amygdala in brain slices from wild type mice but not in mGluR7 knockout mice, thus suggesting XAP044 specific action on mGluR7 [43]. *In vivo* experiments have shown that XAP044 is brain

penetrant and, similar to mGluR7 knockout mice, produces anti-stress, antidepressant-, and anxiolytic-like effects and reduces freezing in a fear conditioning paradigm [43]. A single systemic XAP044 administration reverted mechanical allodynia and ameliorated anxiety- and depression-like behaviors in a model of neuropathic pain [107]. Interestingly, (+)-6-(2,4-dimethylphenyl)-2-ethyl-6,7-dihydrobenzo [d]oxazol-4(5H)-one (ADX71743), another selective mGluR7 NAM, has demonstrated excellent brain exposure after subcutaneous administration and anxiolytic-like effects in the elevated plus maze and marble burying tests. Further, ADX71743 also reduced amphetamine-induced hyperactivity without altering baseline locomotor activity [109]. The recent development of selective mGluR7 NAMs has profoundly contributed to the delineation of a functional role for mGluR7 in physiological and pathological conditions. Apart from providing a better understanding of mGluR7 function at the synapse, mGluR7 NAMs have exhibited consistent results, unlike previous ligands like AMN082. Indeed MMPIP, XAP044, and ADX71743 have demonstrated selectivity for mGluR7 and behavioral effects in line with the mGluR7-knockout phenotype. MMPIP and XAP044 have also been tested in chronic pain conditions and co-morbid affective and cognitive disorders, thus their possible therapeutic exploitation is reasonable. A summary of mGluR7 positive and negative allosteric modulators effects is presented in Table 1.

CONCLUSIONS

The greater importance of mGluR7 of all mGluRs is unveiled by its wide distribution and its high evolutionary conservation. In particular, mGluR7 exhibits high expression in excitatory and inhibitory synapses within the brain, which are considered critical for neurologic and pathologic disorders. Being modulators of these synapses, mGluR7 ligands have a limitless potential. Initial studies using mGluR7-knockout mice have suggested that mGluR7 is involved in a series of neurological and psychiatric disorders such as epilepsy, anxiety, and depression. These effects were later confirmed by similar findings obtained using selective mGluR7 allosteric modulators. Moreover, some of the novel mGluR7 negative allosteric modulators, apart from clarifying the function of mGluR7 in fine tuning excitatory and inhibitory synapses within the CNS, have confirmed the mGluR7-knockout phenotype and clarified the role of mGluR7 in neuropsychiatric disorders. In this context, MMPIP and XAP044 have also been tested in models of neuropathic pain and have shown promising anti-allodynic, anti-anxiety-, and anti-depressant-like effects. Further, these compounds have been reported to improve cognitive performance, which is deeply affected in these models of chronic pain. As a direct consequence of these findings, further studies investigating mGluR7 negative allosteric modulator effects are expected to facilitate development of novel therapeutics for pain and pain-related affective and cognitive disorders.

CONFLICT OF INTEREST

All the authors have read and approved the paper and have not any financial or other relationships that might lead to a conflict of interest.

ACKNOWLEDGEMENTS

The Authors thank the Italian Ministero dell'Istruzione, Università e della Ricerca (PRIN 2012 and FIRB 2012) for supporting their research.

REFERENCES

- Conn, P.J.; Pin, J.P. Pharmacology and functions of metabotropic glutamate receptors. *Annu. Rev. Pharmacol. Toxicol.*, **1997**, *37*, 205-237. [<http://dx.doi.org/10.1146/annurev.pharmtox.37.1.205>] [PMID: 9131252]
- Swanson, C.J.; Bures, M.; Johnson, M.P.; Linden, A.M.; Monn, J.A.; Schoepp, D.D. Metabotropic glutamate receptors as novel targets for anxiety and stress disorders. *Nat. Rev. Drug Discov.*, **2005**, *4*(2), 131-144. [<http://dx.doi.org/10.1038/nrd1630>] [PMID: 15665858]
- Ferraguti, F.; Shigemoto, R. Metabotropic glutamate receptors. *Cell Tissue Res.*, **2006**, *326*(2), 483-504. [<http://dx.doi.org/10.1007/s00441-006-0266-5>] [PMID: 16847639]
- Ritter, S.L.; Hall, R.A. Fine-tuning of GPCR activity by receptor-interacting proteins. *Nat. Rev. Mol. Cell Biol.*, **2009**, *10*(12), 819-830. [<http://dx.doi.org/10.1038/nrm2803>] [PMID: 19935667]
- Shigemoto, R.; Kulik, A.; Roberts, J.D.; Ohishi, H.; Nusser, Z.; Kaneko, T.; Somogyi, P. Target-cell-specific concentration of a metabotropic glutamate receptor in the presynaptic active zone. *Nature*, **1996**, *381*(6582), 523-525. [<http://dx.doi.org/10.1038/381523a0>] [PMID: 8632825]
- D'Antoni, S.; Berretta, A.; Bonaccorso, C.M.; Bruno, V.; Aronica, E.; Nicoletti, F.; Catania, M.V. Metabotropic glutamate receptors in glial cells. *Neurochem. Res.*, **2008**, *33*(12), 2436-2443. [<http://dx.doi.org/10.1007/s11064-008-9694-9>] [PMID: 18438710]
- Ohishi, H.; Akazawa, C.; Shigemoto, R.; Nakanishi, S.; Mizuno, N. Distributions of the mRNAs for L-2-amino-4-phosphonobutyrate-sensitive metabotropic glutamate receptors, mGluR4 and mGluR7, in the rat brain. *J. Comp. Neurol.*, **1995**, *360*(4), 555-570. [<http://dx.doi.org/10.1002/cne.903600402>] [PMID: 8801249]
- Petralia, R.S.; Wang, Y.X.; Niedzielski, A.S.; Wenthold, R.J. The metabotropic glutamate receptors, mGluR2 and mGluR3, show unique postsynaptic, presynaptic and glial localizations. *Neuroscience*, **1996**, *71*(4), 949-976. [[http://dx.doi.org/10.1016/0306-4522\(95\)00533-1](http://dx.doi.org/10.1016/0306-4522(95)00533-1)] [PMID: 8684625]
- Vardi, N.; Duvoisin, R.; Wu, G.; Sterling, P. Localization of mGluR6 to dendrites of ON bipolar cells in primate retina. *J. Comp. Neurol.*, **2000**, *423*(3), 402-412. [[http://dx.doi.org/10.1002/1096-9861\(20000731\)423:3<402::AID-CNE4>3.0.CO;2-E](http://dx.doi.org/10.1002/1096-9861(20000731)423:3<402::AID-CNE4>3.0.CO;2-E)] [PMID: 10870081]
- Cajina, M.; Nattini, M.; Song, D.; Smagin, G.; Jørgensen, E.B.; Chandrasena, G.; Bundgaard, C.; Toft, D.B.; Huang, X.; Acher, F.; Doller, D. Qualification of LSP1-2111 as a Brain Penetrant Group III Metabotropic Glutamate Receptor Orthosteric Agonist. *ACS Med. Chem. Lett.*, **2014**, *5*(2), 119-123. [<http://dx.doi.org/10.1021/ml400338f>] [PMID: 24900783]
- Kinzie, J.M.; Saugstad, J.A.; Westbrook, G.L.; Segerson, T.P. Distribution of metabotropic glutamate receptor 7 messenger RNA in the developing and adult rat brain. *Neuroscience*, **1995**, *69*(1), 167-176. [[http://dx.doi.org/10.1016/0306-4522\(95\)00244-D](http://dx.doi.org/10.1016/0306-4522(95)00244-D)] [PMID: 8637615]
- Corti, C.; Restituito, S.; Rimland, J.M.; Brabet, I.; Corsi, M.; Pin, J.P.; Ferraguti, F. Cloning and characterization of alternative mRNA forms for the rat metabotropic glutamate receptors mGluR7 and mGluR8. *Eur. J. Neurosci.*, **1998**, *10*(12), 3629-3641. [<http://dx.doi.org/10.1046/j.1460-9568.1998.00371.x>] [PMID: 9875342]
- Bradley, S.R.; Levey, A.I.; Hersch, S.M.; Conn, P.J. Immunocytochemical localization of group III metabotropic glutamate receptors in the hippocampus with subtype-specific antibodies. *J. Neurosci.*, **1996**, *16*(6), 2044-2056. [PMID: 8604049]
- Shigemoto, R.; Kinoshita, A.; Wada, E.; Nomura, S.; Ohishi, H.; Takada, M.; Flor, P.J.; Neki, A.; Abe, T.; Nakanishi, S.; Mizuno, N. Differential presynaptic localization of metabotropic glutamate receptor subtypes in the rat hippocampus. *J. Neurosci.*, **1997**, *17*(19), 7503-7522. [PMID: 9295396]
- Wada, E.; Shigemoto, R.; Kinoshita, A.; Ohishi, H.; Mizuno, N. Metabotropic glutamate receptor subtypes in axon terminals of

- projection fibers from the main and accessory olfactory bulbs: a light and electron microscopic immunohistochemical study in the rat. *J. Comp. Neurol.*, **1998**, *393*(4), 493-504. [http://dx.doi.org/10.1002/(SICI)1096-9861(19980420)393:4<493::AID-CNE8>3.0.CO;2-W] [PMID: 9550154]
- [16] Dalezios, Y.; Luján, R.; Shigemoto, R.; Roberts, J.D.; Somogyi, P. Enrichment of mGluR7a in the presynaptic active zones of GABAergic and non-GABAergic terminals on interneurons in the rat somatosensory cortex. *Cereb. Cortex*, **2002**, *12*(9), 961-974. [http://dx.doi.org/10.1093/cercor/12.9.961] [PMID: 12183395]
- [17] Somogyi, P.; Dalezios, Y.; Luján, R.; Roberts, J.D.; Watanabe, M.; Shigemoto, R. High level of mGluR7 in the presynaptic active zones of select populations of GABAergic terminals innervating interneurons in the rat hippocampus. *Eur. J. Neurosci.*, **2003**, *17*(12), 2503-2520. [http://dx.doi.org/10.1046/j.1460-9568.2003.02697.x] [PMID: 12823458]
- [18] Martín, R.; Durroux, T.; Ciruela, F.; Torres, M.; Pin, J.P.; Sánchez-Prieto, J. The metabotropic glutamate receptor mGlu7 activates phospholipase C, translocates munc-13-1 protein, and potentiates glutamate release at cerebrocortical nerve terminals. *J. Biol. Chem.*, **2010**, *285*(23), 17907-17917. [http://dx.doi.org/10.1074/jbc.M109.080838] [PMID: 20375012]
- [19] Kosinski, C.M.; Risso Bradley, S.; Conn, P.J.; Levey, A.I.; Landwehrmeyer, G.B.; Penney, J.B., Jr; Young, A.B.; Standaert, D.G. Localization of metabotropic glutamate receptor 7 mRNA and mGluR7a protein in the rat basal ganglia. *J. Comp. Neurol.*, **1999**, *415*(2), 266-284. [http://dx.doi.org/10.1002/(SICI)1096-9861(19991213)415:2<266::AID-CNE9>3.0.CO;2-7] [PMID: 10545164]
- [20] Brandstätter, J.H.; Koulou, P.; Kuhn, R.; van der Putten, H.; Wässle, H. Compartmental localization of a metabotropic glutamate receptor (mGluR7): two different active sites at a retinal synapse. *J. Neurosci.*, **1996**, *16*(15), 4749-4756. [PMID: 8764662]
- [21] Kinzie, J.M.; Shinohara, M.M.; van den Pol, A.N.; Westbrook, G.L.; Segerson, T.P. Immunolocalization of metabotropic glutamate receptor 7 in the rat olfactory bulb. *J. Comp. Neurol.*, **1997**, *385*(3), 372-384. [http://dx.doi.org/10.1002/(SICI)1096-9861(19970901)385:3<372::AID-CNE3>3.0.CO;2-0] [PMID: 9300765]
- [22] Gu, Z.; Liu, W.; Wei, J.; Yan, Z. Regulation of N-methyl-D-aspartic acid (NMDA) receptors by metabotropic glutamate receptor 7. *J. Biol. Chem.*, **2012**, *287*(13), 10265-10275. [http://dx.doi.org/10.1074/jbc.M111.325175] [PMID: 22287544]
- [23] Flor, P.J.; Van Der Putten, H.; Rüegg, D.; Lukic, S.; Leonhardt, T.; Bence, M.; Sansig, G.; Knöpfel, T.; Kuhn, R. A novel splice variant of a metabotropic glutamate receptor, human mGluR7b. *Neuropharmacology*, **1997**, *36*(2), 153-159. [http://dx.doi.org/10.1016/S0028-3908(96)00176-1] [PMID: 9144652]
- [24] Kinoshita, A.; Shigemoto, R.; Ohishi, H.; van der Putten, H.; Mizuno, N. 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.*, **1998**, *393*(3), 332-352. [http://dx.doi.org/10.1002/(SICI)1096-9861(19980413)393:3<332::AID-CNE6>3.0.CO;2-2] [PMID: 9548554]
- [25] Schulz, H.L.; Stohr, H.; Weber, B.H. Characterization of three novel isoforms of the metabotropic glutamate receptor 7 (GRM7). *Neurosci. Lett.*, **2002**, *326*(1), 37-40. [http://dx.doi.org/10.1016/S0304-3940(02)00306-3] [PMID: 12052533]
- [26] Julio-Pieper, M.; Hyland, N.P.; Bravo, J.A.; Dinan, T.G.; Cryan, J.F. A novel role for the metabotropic glutamate receptor-7: modulation of faecal water content and colonic electrolyte transport in the mouse. *Br. J. Pharmacol.*, **2010**, *160*(2), 367-375. [http://dx.doi.org/10.1111/j.1476-5381.2010.00713.x] [PMID: 20423346]
- [27] Nakamura, E.; Hasumura, M.; San Gabriel, A.; Uneyama, H.; Torii, K. New frontiers in gut nutrient sensor research: luminal glutamate-sensing cells in rat gastric mucosa. *J. Pharmacol. Sci.*, **2010**, *112*(1), 13-18. [http://dx.doi.org/10.1254/jphs.09R16FM] [PMID: 20093783]
- [28] Scaccianoce, S.; Matrisciano, F.; Del Bianco, P.; Caricasole, A.; Di Giorgi Gerevini, V.; Cappuccio, I.; Melchiorri, D.; Battaglia, G.; Nicoletti, F. Endogenous activation of group-II metabotropic glutamate receptors inhibits the hypothalamic-pituitary-adrenocortical axis. *Neuropharmacology*, **2003**, *44*(5), 555-561. [http://dx.doi.org/10.1016/S0028-3908(03)00027-3] [PMID: 12668041]
- [29] Friedman, R.A.; Van Laer, L.; Huentelman, M.J.; Sheth, S.S.; Van Eyken, E.; Corneveaux, J.J.; Tempe, W.D.; Halperin, R.F.; Thorburn, A.Q.; Thys, S.; Bonneux, S.; Franssen, E.; Huyghe, J.; Pyykkö, I.; Cremers, C.W.; Kremer, H.; Dhooge, I.; Stephens, D.; Orzan, E.; Pfister, M.; Bille, M.; Parving, A.; Sorri, M.; Van de Heyning, P.H.; Makmura, L.; Ohmen, J.D.; Linthicum, F.H., Jr; Fayad, J.N.; Pearson, J.V.; Craig, D.W.; Stephan, D.A.; Van Camp, G. GRM7 variants confer susceptibility to age-related hearing impairment. *Hum. Mol. Genet.*, **2009**, *18*(4), 785-796. [http://dx.doi.org/10.1093/hmg/ddn402] [PMID: 19047183]
- [30] Schoepp, D.D.; Jane, D.E.; Monn, J.A. Pharmacological agents acting at subtypes of metabotropic glutamate receptors. *Neuropharmacology*, **1999**, *38*(10), 1431-1476. [http://dx.doi.org/10.1016/S0028-3908(99)00092-1] [PMID: 10530808]
- [31] Millán, C.; Luján, R.; Shigemoto, R.; Sánchez-Prieto, J. The inhibition of glutamate release by metabotropic glutamate receptor 7 affects both [Ca²⁺]_i and cAMP: evidence for a strong reduction of Ca²⁺ entry in single nerve terminals. *J. Biol. Chem.*, **2002**, *277*(16), 14092-14101. [http://dx.doi.org/10.1074/jbc.M109044200] [PMID: 11825890]
- [32] Laezza, F.; Doherty, J.J.; Dingledine, R. Long-term depression in hippocampal interneurons: joint requirement for pre- and post-synaptic events. *Science*, **1999**, *285*(5432), 1411-1414. [http://dx.doi.org/10.1126/science.285.5432.1411] [PMID: 10464102]
- [33] Kogo, N.; Dalezios, Y.; Capogna, M.; Ferraguti, F.; Shigemoto, R.; Somogyi, P. Depression of GABAergic input to identified hippocampal neurons by group III metabotropic glutamate receptors in the rat. *Eur. J. Neurosci.*, **2004**, *19*(10), 2727-2740. [http://dx.doi.org/10.1111/j.0953-816X.2004.03394.x] [PMID: 15147307]
- [34] Pelkey, K.A.; Lavezzari, G.; Racca, C.; Roche, K.W.; McBain, C.J. mGluR7 is a metaplastic switch controlling bidirectional plasticity of feedforward inhibition. *Neuron*, **2005**, *46*(1), 89-102. [http://dx.doi.org/10.1016/j.neuron.2005.02.011] [PMID: 15820696]
- [35] Ayala, J.E.; Niswender, C.M.; Luo, Q.; Banko, J.L.; Conn, P.J. Group III mGluR regulation of synaptic transmission at the SC-CA1 synapse is developmentally regulated. *Neuropharmacology*, **2008**, *54*(5), 804-814. [http://dx.doi.org/10.1016/j.neuropharm.2007.12.009] [PMID: 18255102]
- [36] Turner, J.P.; Salt, T.E. Group II and III metabotropic glutamate receptors and the control of the nucleus reticularis thalami input to rat thalamocortical neurones *in vitro*. *Neuroscience*, **2003**, *122*(2), 459-469. [http://dx.doi.org/10.1016/j.neuroscience.2003.08.014] [PMID: 14614910]
- [37] Kyuyoung, C.L.; Huguenard, J.R. Modulation of short-term plasticity in the corticothalamic circuit by group III metabotropic glutamate receptors. *J. Neurosci.*, **2014**, *34*(2), 675-687. [http://dx.doi.org/10.1523/JNEUROSCI.1477-13.2014] [PMID: 24403165]
- [38] Xi, Z.X.; Shen, H.; Baker, D.A.; Kalivas, P.W. Inhibition of non-vesicular glutamate release by group III metabotropic glutamate receptors in the nucleus accumbens. *J. Neurochem.*, **2003**, *87*(5), 1204-1212. [http://dx.doi.org/10.1046/j.1471-4159.2003.02093.x] [PMID: 14622100]
- [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*, **2008**, *54*(3), 542-551. [http://dx.doi.org/10.1016/j.neuropharm.2007.11.005] [PMID: 18155073]
- [40] Marabese, I.; Rossi, F.; Palazzo, E.; de Novellis, V.; Starowicz, K.; Cristiano, L.; Vita, D.; Gatta, L.; Guida, F.; Di Marzo, V.; Rossi, F.; Maione, S. Periaqueductal gray metabotropic glutamate receptor subtype 7 and 8 mediate opposite effects on amino acid release, rostral ventromedial medulla cell activities, and thermal nociception. *J. Neurophysiol.*, **2007**, *98*(1), 43-53. [http://dx.doi.org/10.1152/jn.00356.2007] [PMID: 17507496]
- [41] Ugolini, A.; Large, C.H.; Corsi, M. AMN082, an allosteric mGluR7 agonist that inhibits afferent glutamatergic transmission in rat basolateral amygdala. *Neuropharmacology*, **2008**, *55*(4), 532-536. [http://dx.doi.org/10.1016/j.neuropharm.2008.04.020] [PMID: 18533198]
- [42] Ren, W.; Palazzo, E.; Maione, S.; Neugebauer, V. Differential effects of mGluR7 and mGluR8 activation on pain-related synaptic activity in the amygdala. *Neuropharmacology*, **2011**, *61*(8), 1334-1344. [http://dx.doi.org/10.1016/j.neuropharm.2011.08.006] [PMID: 21854791]
- [43] Gee, C.E.; Peterlik, D.; Neuhäuser, C.; Bouhelal, R.; Kaupmann, K.; Laue, G.; Uschold-Schmidt, N.; Feuerbach, D.; Zimmermann,

- K.; Ofner, S.; Cryan, J.F.; van der Putten, H.; Fendt, M.; Vranesic, I.; Glatthar, R.; Flor, P.J. Blocking metabotropic glutamate receptor subtype 7 (mGlu7) via the Venus flytrap domain (VFTD) inhibits amygdala plasticity, stress, and anxiety-related behavior. *J. Biol. Chem.*, **2014**, *289*(16), 10975-10987. [http://dx.doi.org/10.1074/jbc.M113.542654] [PMID: 24596089]
- [44] Perroy, J.; Prezeau, L.; De Waard, M.; Shigemoto, R.; Bockaert, J.; Fagni, L. Selective blockade of P/Q-type calcium channels by the metabotropic glutamate receptor type 7 involves a phospholipase C pathway in neurons. *J. Neurosci.*, **2000**, *20*(21), 7896-7904. [PMID: 11050109]
- [45] Takahashi, T.; Forsythe, I.D.; Tsujimoto, T.; Barnes-Davies, M.; Onodera, K. Presynaptic calcium current modulation by a metabotropic glutamate receptor. *Science*, **1996**, *274*(5287), 594-597. [http://dx.doi.org/10.1126/science.274.5287.594] [PMID: 8849448]
- [46] Pelkey, K.A.; Topolnik, L.; Lacaille, J.C.; McBain, C.J. Compartmentalized Ca(2+) channel regulation at divergent mossy-fiber release sites underlies target cell-dependent plasticity. *Neuron*, **2006**, *52*(3), 497-510. [http://dx.doi.org/10.1016/j.neuron.2006.08.032] [PMID: 17088215]
- [47] Martín, R.; Torres, M.; Sánchez-Prieto, J. mGluR7 inhibits glutamate release through a PKC-independent decrease in the activity of P/Q-type Ca²⁺ channels and by diminishing cAMP in hippocampal nerve terminals. *Eur. J. Neurosci.*, **2007**, *26*(2), 312-322. [http://dx.doi.org/10.1111/j.1460-9568.2007.05660.x] [PMID: 17650109]
- [48] Saugstad, J.A.; Segerson, T.P.; Westbrook, G.L. Metabotropic glutamate receptors activate G-protein-coupled inwardly rectifying potassium channels in *Xenopus* oocytes. *J. Neurosci.*, **1996**, *16*(19), 5979-5985. [PMID: 8815880]
- [49] Nakajima, Y.; Yamamoto, T.; Nakayama, T.; Nakanishi, S. A relationship between protein kinase C phosphorylation and calmodulin binding to the metabotropic glutamate receptor subtype 7. *J. Biol. Chem.*, **1999**, *274*(39), 27573-27577. [http://dx.doi.org/10.1074/jbc.274.39.27573] [PMID: 10488094]
- [50] Macek, T.A.; Schaffhauser, H.; Conn, P.J. Protein kinase C and A3 adenosine receptor activation inhibit presynaptic metabotropic glutamate receptor (mGluR) function and uncouple mGluRs from GTP-binding proteins. *J. Neurosci.*, **1998**, *18*(16), 6138-6146. [PMID: 9698308]
- [51] Suh, Y.H.; Pelkey, K.A.; Lavezzari, G.; Roche, P.A.; Huganir, R.L.; McBain, C.J.; Roche, K.W. Corequirement of PICK1 binding and PKC phosphorylation for stable surface expression of the metabotropic glutamate receptor mGluR7. *Neuron*, **2008**, *58*(5), 736-748. [http://dx.doi.org/10.1016/j.neuron.2008.03.028] [PMID: 18549785]
- [52] Suh, Y.H.; Park, J.Y.; Park, S.; Jou, I.; Roche, P.A.; Roche, K.W. Regulation of metabotropic glutamate receptor 7 (mGluR7) internalization and surface expression by Ser/Thr protein phosphatase 1. *J. Biol. Chem.*, **2013**, *288*(24), 17544-17551. [http://dx.doi.org/10.1074/jbc.M112.439513] [PMID: 23612982]
- [53] Bertaso, F.; Zhang, C.; Scheschonka, A.; de Bock, F.; Fontanaud, P.; Marin, P.; Huganir, R.L.; Betz, H.; Bockaert, J.; Fagni, L.; Lerner-Natoli, M. PICK1 uncoupling from mGluR7a causes absence-like seizures. *Nat. Neurosci.*, **2008**, *11*(8), 940-948. [http://dx.doi.org/10.1038/nn.2142] [PMID: 18641645]
- [54] Tomioka, N.H.; Yasuda, H.; Miyamoto, H.; Hatayama, M.; Morimura, N.; Matsumoto, Y.; Suzuki, T.; Odagawa, M.; Odaka, Y.S.; Iwayama, Y.; Won Um, J.; Ko, J.; Inoue, Y.; Kaneko, S.; Hirose, S.; Yamada, K.; Yoshikawa, T.; Yamakawa, K.; Aruga, J. Elfn1 recruits presynaptic mGluR7 in trans and its loss results in seizures. *Nat. Commun.*, **2014**, *5*, 4501. [http://dx.doi.org/10.1038/ncomms5501] [PMID: 25047565]
- [55] Gu, Z.; Cheng, J.; Zhong, P.; Qin, L.; Liu, W.; Yan, Z. Aβ selectively impairs mGluR7 modulation of NMDA signaling in basal forebrain cholinergic neurons: implication in Alzheimer's disease. *J. Neurosci.*, **2014**, *34*(41), 13614-13628. [http://dx.doi.org/10.1523/JNEUROSCI.1204-14.2014] [PMID: 25297090]
- [56] Sansig, G.; Bushell, T.J.; Clarke, V.R.; Rozov, A.; Burnashev, N.; Portet, C.; Gasparini, F.; Schmutz, M.; Klebs, K.; Shigemoto, R.; Flor, P.J.; Kuhn, R.; Knoepfel, T.; Schroeder, M.; Hampson, D.R.; Collett, V.J.; Zhang, C.; Duvoisin, R.M.; Collingridge, G.L.; van Der Putten, H. Increased seizure susceptibility in mice lacking metabotropic glutamate receptor 7. *J. Neurosci.*, **2001**, *21*(22), 8734-8745. [PMID: 11698585]
- [57] Bushell, T.J.; Sansig, G.; Collett, V.J.; van der Putten, H.; Collingridge, G.L. Altered short-term synaptic plasticity in mice lacking the metabotropic glutamate receptor mGlu7. *Scientific WorldJournal*, **2002**, *2*, 730-737. [http://dx.doi.org/10.1100/tsw.2002.146] [PMID: 12805997]
- [58] Hölscher, C.; Schmid, S.; Pilz, P.K.; Sansig, G.; van der Putten, H.; Plappert, C.F. Lack of the metabotropic glutamate receptor subtype 7 selectively impairs short-term working memory but not long-term memory. *Behav. Brain Res.*, **2004**, *154*(2), 473-481. [http://dx.doi.org/10.1016/j.bbr.2004.03.015] [PMID: 15313036]
- [59] Hölscher, C.; Schmid, S.; Pilz, P.K.; Sansig, G.; van der Putten, H.; Plappert, C.F. Lack of the metabotropic glutamate receptor subtype 7 selectively modulates Theta rhythm and working memory. *Learn. Mem.*, **2005**, *12*(5), 450-455. [http://dx.doi.org/10.1101/lm.98305] [PMID: 16204199]
- [60] O'Connor, R.M.; Finger, B.C.; Flor, P.J.; Cryan, J.F. Metabotropic glutamate receptor 7: at the interface of cognition and emotion. *Eur. J. Pharmacol.*, **2010**, *639*(1-3), 123-131. [http://dx.doi.org/10.1016/j.ejphar.2010.02.059] [PMID: 20371242]
- [61] Goddyn, H.; Callaerts-Vegh, Z.; Stroobants, S.; Dirix, T.; Vansteenwegen, D.; Hermans, D.; van der Putten, H.; D'Hooge, R. Deficits in acquisition and extinction of conditioned responses in mGluR7 knockout mice. *Neurobiol. Learn. Mem.*, **2008**, *90*(1), 103-111. [http://dx.doi.org/10.1016/j.nlm.2008.01.001] [PMID: 18289889]
- [62] Callaerts-Vegh, Z.; Beckers, T.; Ball, S.M.; Baeyens, F.; Callaerts, P.F.; Cryan, J.F.; Molnar, E.; D'Hooge, R. Concomitant deficits in working memory and fear extinction are functionally dissociated from reduced anxiety in metabotropic glutamate receptor 7-deficient mice. *J. Neurosci.*, **2006**, *26*(24), 6573-6582. [http://dx.doi.org/10.1523/JNEUROSCI.1497-06.2006] [PMID: 16775145]
- [63] Bouton, M.E.; Moody, E.W. Memory processes in classical conditioning. *Neurosci. Biobehav. Rev.*, **2004**, *28*(7), 663-674. [http://dx.doi.org/10.1016/j.neubiorev.2004.09.001] [PMID: 15555676]
- [64] Kim, J.J.; Rison, R.A.; Fanselow, M.S. Effects of amygdala, hippocampus, and periaqueductal gray lesions on short- and long-term contextual fear. *Behav. Neurosci.*, **1993**, *107*(6), 1093-1098. [http://dx.doi.org/10.1037/0735-7044.107.6.1093] [PMID: 8136063]
- [65] Yamamoto, T.; Shimura, T.; Sako, N.; Yasoshima, Y.; Sakai, N. Neural substrates for conditioned taste aversion in the rat. *Behav. Brain Res.*, **1994**, *65*(2), 123-137. [http://dx.doi.org/10.1016/0166-4328(94)90097-3] [PMID: 7718144]
- [66] Masugi, M.; Yokoi, M.; Shigemoto, R.; Muguruma, K.; Watanabe, Y.; Sansig, G.; van der Putten, H.; Nakanishi, S. Metabotropic glutamate receptor subtype 7 ablation causes deficit in fear response and conditioned taste aversion. *J. Neurosci.*, **1999**, *19*(3), 955-963. [PMID: 9920659]
- [67] Cryan, J.F.; Kelly, P.H.; Neijt, H.C.; Sansig, G.; Flor, P.J.; van Der Putten, H. Antidepressant and anxiolytic-like effects in mice lacking the group III metabotropic glutamate receptor mGluR7. *Eur. J. Neurosci.*, **2003**, *17*(11), 2409-2417. [http://dx.doi.org/10.1046/j.1460-9568.2003.02667.x] [PMID: 12814372]
- [68] Stachowicz, K.; Brański, P.; Klak, K.; van der Putten, H.; Cryan, J.F.; Flor, P.J.; Andrzej, P. Selective activation of metabotropic G-protein-coupled glutamate 7 receptor elicits anxiolytic-like effects in mice by modulating GABAergic neurotransmission. *Behav. Pharmacol.*, **2008**, *19*(5-6), 597-603. [http://dx.doi.org/10.1097/FBP.0b013e32830cd839] [PMID: 18690114]
- [69] Fendt, M.; Imobersteg, S.; Peterlik, D.; Chaperon, F.; Mattes, C.; Wittmann, C.; Olpe, H.R.; Mosbacher, J.; Vranesic, I.; van der Putten, H.; McAllister, K.H.; Flor, P.J.; Gee, C.E. Differential roles of mGlu(7) and mGlu(8) in amygdala-dependent behavior and physiology. *Neuropharmacology*, **2013**, *72*, 215-223. [http://dx.doi.org/10.1016/j.neuropharm.2013.04.052] [PMID: 23664812]
- [70] Mitsukawa, K.; Mombereau, C.; Lötscher, E.; Uzunov, D.P.; van der Putten, H.; Flor, P.J.; Cryan, J.F. 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*, **2006**, *31*(6), 1112-1122. [PMID: 16237391]
- [71] Holsboer, F.; Barden, N. Antidepressants and hypothalamic-pituitary-adrenocortical regulation. *Endocr. Rev.*, **1996**, *17*(2), 187-205. [http://dx.doi.org/10.1210/edrv-17-2-187] [PMID: 8706631]
- [72] Barden, N. Implication of the hypothalamic-pituitary-adrenal axis in the physiopathology of depression. *J. Psychiatry Neurosci.*, **2004**, *29*(3), 185-193. [PMID: 15173895]

- [73] Holsboer, F.; Bender, W.; Benkert, O.; Klein, H.E.; Schmauss, M. Diagnostic value of dexamethasone suppression test in depression. *Lancet*, **1980**, 2(8196), 706. [http://dx.doi.org/10.1016/S0140-6736(80)92755-5] [PMID: 6106823]
- [74] Hoshaw, B.A.; Malberg, J.E.; Lucki, I. Central administration of IGF-I and BDNF leads to long-lasting antidepressant-like effects. *Brain Res.*, **2005**, 1037(1-2), 204-208. [http://dx.doi.org/10.1016/j.brainres.2005.01.007] [PMID: 15777771]
- [75] Klak, K.; Palucha, A.; Brański, P.; Sowa, M.; Pilc, A. Combined administration of PHCC, a positive allosteric modulator of mGlu4 receptors and ACPT-I, mGlu III receptor agonist evokes antidepressant-like effects in rats. *Amino Acids*, **2007**, 32(2), 169-172. [http://dx.doi.org/10.1007/s00726-006-0316-z] [PMID: 16868652]
- [76] Lafon-Cazal, M.; Fagni, L.; Guiraud, M.J.; Mary, S.; Lerner-Natoli, M.; Pin, J.P.; Shigemoto, R.; Bockaert, J. mGluR7-like metabotropic glutamate receptors inhibit NMDA-mediated excitotoxicity in cultured mouse cerebellar granule neurons. *Eur. J. Neurosci.*, **1999**, 11(2), 663-672. [http://dx.doi.org/10.1046/j.1460-9568.1999.00475.x] [PMID: 10051767]
- [77] Pin, J.P.; De Colle, C.; Bessis, A.S.; Acher, F. New perspectives for the development of selective metabotropic glutamate receptor ligands. *Eur. J. Pharmacol.*, **1999**, 375(1-3), 277-294. [http://dx.doi.org/10.1016/S0014-2999(99)00258-7] [PMID: 10443583]
- [78] Mitsukawa, K.; Yamamoto, R.; Ofner, S.; Nozulak, J.; Pescott, O.; Lukic, S.; Stoehr, N.; Mombereau, C.; Kuhn, R.; McAllister, K.H.; van der Putten, H.; Cryan, J.F.; Flor, P.J. A selective metabotropic glutamate receptor 7 agonist: activation of receptor signaling via an allosteric site modulates stress parameters *in vivo*. *Proc. Natl. Acad. Sci. USA*, **2005**, 102(51), 18712-18717. [http://dx.doi.org/10.1073/pnas.0508063102] [PMID: 16339898]
- [79] Acher, F.C.; Tellier, F.J.; Azerad, R.; Brabet, I.N.; Fagni, L.; Pin, J.P. Synthesis and pharmacological characterization of aminocyclopentanetricarboxylic acids: new tools to discriminate between metabotropic glutamate receptor subtypes. *J. Med. Chem.*, **1997**, 40(19), 3119-3129. [http://dx.doi.org/10.1021/jm970207b] [PMID: 9301676]
- [80] Palucha-Poniewiera, A.; Klodzińska, A.; Stachowicz, K.; Tokarski, K.; Hess, G.; Schann, S.; Frauli, M.; Neuville, P.; Pilc, A. Peripheral administration of group III mGlu receptor agonist ACPT-I exerts potential antipsychotic effects in rodents. *Neuropharmacology*, **2008**, 55(4), 517-524. [http://dx.doi.org/10.1016/j.neuropharm.2008.06.033] [PMID: 18619473]
- [81] Kingston, A.E.; Ornstein, P.L.; Wright, R.A.; Johnson, B.G.; Mayne, N.G.; Burnett, J.P.; Belagaje, R.; Wu, S.; Schoepp, D.D. LY341495 is a nanomolar potent and selective antagonist of group II metabotropic glutamate receptors. *Neuropharmacology*, **1998**, 37(1), 1-12. [http://dx.doi.org/10.1016/S0028-3908(97)00191-3] [PMID: 9680254]
- [82] Flor, P.J.; Acher, F.C. Orthosteric versus allosteric GPCR activation: the great challenge of group-III mGluRs. *Biochem. Pharmacol.*, **2012**, 84(4), 414-424. [http://dx.doi.org/10.1016/j.bcp.2012.04.013] [PMID: 22554564]
- [83] Sukoff Rizzo, S.J.; Leonard, S.K.; Gilbert, A.; Dollings, P.; Smith, D.L.; Zhang, M.Y.; Di, L.; Platt, B.J.; Neal, S.; Dwyer, J.M.; Bender, C.N.; Zhang, J.; Lock, T.; Kowal, D.; Kramer, A.; Randall, A.; Huselton, C.; Vishwanathan, K.; Tse, S.Y.; Butera, J.; Ring, R.H.; Rosenzweig-Lipson, S.; Hughes, Z.A.; Dunlop, J. The metabotropic glutamate receptor 7 allosteric modulator AMN082: a monoaminergic agent in disguise? *J. Pharmacol. Exp. Ther.*, **2011**, 338(1), 345-352. [http://dx.doi.org/10.1124/jpet.110.177378] [PMID: 21508084]
- [84] Conn, P.J.; Niswender, C.M. mGluR7's lucky number. *Proc. Natl. Acad. Sci. USA*, **2006**, 103(2), 251-252. [http://dx.doi.org/10.1073/pnas.0510051103] [PMID: 16407154]
- [85] Fendt, M.; Schmid, S.; Thakker, D.R.; Jacobson, L.H.; Yamamoto, R.; Mitsukawa, K.; Maier, R.; Natt, F.; Hüsken, D.; Kelly, P.H.; McAllister, K.H.; Hoyer, D.; van der Putten, H.; Cryan, J.F.; Flor, P.J. mGluR7 facilitates extinction of aversive memories and controls amygdala plasticity. *Mol. Psychiatry*, **2008**, 13(10), 970-979. [http://dx.doi.org/10.1038/sj.mp.4002073] [PMID: 17712315]
- [86] Siegl, S.; Flor, P.J.; Fendt, M. Amygdaloid metabotropic glutamate receptor subtype 7 is involved in the acquisition of conditioned fear. *Neuroreport*, **2008**, 19(11), 1147-1150. [http://dx.doi.org/10.1097/WNR.0b013e328307f295] [PMID: 18596617]
- [87] Mickley, G.A.; Kenmuir, C.L.; Yocom, A.M.; Wellman, J.A.; Biada, J.M. A role for prefrontal cortex in the extinction of a conditioned taste aversion. *Brain Res.*, **2005**, 1051(1-2), 176-182. [http://dx.doi.org/10.1016/j.brainres.2005.05.033] [PMID: 15961067]
- [88] Palazzo, E.; Fu, Y.; Ji, G.; Maione, S.; Neugebauer, V. Group III mGluR7 and mGluR8 in the amygdala differentially modulate nocifensive and affective pain behaviors. *Neuropharmacology*, **2008**, 55(4), 537-545. [http://dx.doi.org/10.1016/j.neuropharm.2008.05.007] [PMID: 18533199]
- [89] Palucha, A.; Klak, K.; Branski, P.; van der Putten, H.; Flor, P.J.; Pilc, A. Activation of the mGlu7 receptor elicits antidepressant-like effects in mice. *Psychopharmacology (Berl.)*, **2007**, 194(4), 555-562. [http://dx.doi.org/10.1007/s00213-007-0856-2] [PMID: 17622518]
- [90] Dobi, A.; Sartori, S.B.; Busti, D.; Van der Putten, H.; Singewald, N.; Shigemoto, R.; Ferraguti, F. Neural substrates for the distinct effects of presynaptic group III metabotropic glutamate receptors on extinction of contextual fear conditioning in mice. *Neuropharmacology*, **2013**, 66, 274-289. [http://dx.doi.org/10.1016/j.neuropharm.2012.05.025] [PMID: 22643400]
- [91] Palucha, A.; Pilc, A. Metabotropic glutamate receptor ligands as possible anxiolytic and antidepressant drugs. *Pharmacol. Ther.*, **2007**, 115(1), 116-147. [http://dx.doi.org/10.1016/j.pharmthera.2007.04.007] [PMID: 17582504]
- [92] Bradley, S.R.; Uslander, J.M.; Flick, R.B.; Lee, A.; Groover, K.M.; Hutson, P.H. The mGluR7 allosteric agonist AMN082 produces antidepressant-like effects by modulating glutamatergic signaling. *Pharmacol. Biochem. Behav.*, **2012**, 101(1), 35-40. [http://dx.doi.org/10.1016/j.pbb.2011.11.006] [PMID: 22138407]
- [93] Liu, X.H.; Han, M.; Zhu, J.X.; Sun, N.; Tang, J.S.; Huo, F.Q.; Li, J.; Xu, F.Y.; Du, J.Q. Metabotropic glutamate subtype 7 and 8 receptors oppositely modulate cardiac nociception in the rat nucleus tractus solitarius. *Neuroscience*, **2012**, 220, 322-329. [http://dx.doi.org/10.1016/j.neuroscience.2012.05.024] [PMID: 22617702]
- [94] Ferrante, M.; Migliore, M.; Ascoli, G.A. Feed-forward inhibition as a buffer of the neuronal input-output relation. *Proc. Natl. Acad. Sci. USA*, **2009**, 106(42), 18004-18009. [http://dx.doi.org/10.1073/pnas.0904784106] [PMID: 19815518]
- [95] Goudet, C.; Chapuy, E.; Alloui, A.; Acher, F.; Pin, J.P.; Eschaliier, A. Group III metabotropic glutamate receptors inhibit hyperalgesia in animal models of inflammation and neuropathic pain. *Pain*, **2008**, 137(1), 112-124. [http://dx.doi.org/10.1016/j.pain.2007.08.020] [PMID: 17900808]
- [96] Heinricher, M.M.; Tortorici, V. Interference with GABA transmission in the rostral ventromedial medulla: disinhibition of off-cells as a central mechanism in nociceptive modulation. *Neuroscience*, **1994**, 63(2), 533-546. [http://dx.doi.org/10.1016/0306-4522(94)90548-7] [PMID: 7891863]
- [97] G, S.; Suvarna, P.; Hadigal, S.; Kamath, P.; Prabhu, N.; Shenoy K, A.; Lc, P. Can Metabotropic Glutamate Receptor 7 (mGluR 7) be a Novel Target for Analgesia? *J. Clin. Diagn. Res.*, **2014**, 8(9), HC16-HC18. [PMID: 25386457]
- [98] Osikowicz, M.; Mika, J.; Makuch, W.; Przewlocka, B. Glutamate receptor ligands attenuate allodynia and hyperalgesia and potentiate morphine effects in a mouse model of neuropathic pain. *Pain*, **2008**, 139(1), 117-126. [http://dx.doi.org/10.1016/j.pain.2008.03.017] [PMID: 18442882]
- [99] Dolan, S.; Gunn, M.D.; Crossan, C.; Nolan, A.M. Activation of metabotropic glutamate receptor 7 in spinal cord inhibits pain and hyperalgesia in a novel formalin model in sheep. *Behav. Pharmacol.*, **2011**, 22(5-6), 582-588. [http://dx.doi.org/10.1097/FBP.0b013e3283478802] [PMID: 21597362]
- [100] Pelkey, K.A.; Yuan, X.; Lavezzi, G.; Roche, K.W.; McBain, C.J. mGluR7 undergoes rapid internalization in response to activation by the allosteric agonist AMN082. *Neuropharmacology*, **2007**, 52(1), 108-117. [http://dx.doi.org/10.1016/j.neuropharm.2006.07.020] [PMID: 16914173]
- [101] Bahi, A.; Fizia, K.; Dietz, M.; Gasparini, F.; Flor, P.J. Pharmacological modulation of mGluR7 with AMN082 and MMPIP exerts specific influences on alcohol consumption and preference in rats. *Addict. Biol.*, **2012**, 17(2), 235-247. [http://dx.doi.org/10.1111/j.1369-1600.2010.00310.x] [PMID: 21392179]

- [102] Li, X.; Xi, Z.X.; Markou, A. Metabotropic glutamate 7 (mGlu7) receptor: a target for medication development for the treatment of cocaine dependence. *Neuropharmacology*, **2013**, *66*, 12-23. [http://dx.doi.org/10.1016/j.neuropharm.2012.04.010] [PMID: 22546614]
- [103] Suzuki, G.; Tsukamoto, N.; Fushiki, H.; Kawagishi, A.; Nakamura, M.; Kurihara, H.; Mitsuya, M.; Ohkubo, M.; Ohta, H. *In vitro* pharmacological characterization of novel isoxazopyridone derivatives as allosteric metabotropic glutamate receptor 7 antagonists. *J. Pharmacol. Exp. Ther.*, **2007**, *323*(1), 147-156. [http://dx.doi.org/10.1124/jpet.107.124701] [PMID: 17609420]
- [104] Nakamura, M.; Kurihara, H.; Suzuki, G.; Mitsuya, M.; Ohkubo, M.; Ohta, H. Isoxazopyridone derivatives as allosteric metabotropic glutamate receptor 7 antagonists. *Bioorg. Med. Chem. Lett.*, **2010**, *20*(2), 726-729. [http://dx.doi.org/10.1016/j.bmcl.2009.11.070] [PMID: 20005101]
- [105] Hikichi, H.; Murai, T.; Okuda, S.; Maehara, S.; Satow, A.; Ise, S.; Nishino, M.; Suzuki, G.; Takehana, H.; Hata, M.; Ohta, H. 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.*, **2010**, *639*(1-3), 106-114. [http://dx.doi.org/10.1016/j.ejphar.2009.08.047] [PMID: 20371227]
- [106] Palazzo, E.; Marabese, I.; Luongo, L.; Boccella, S.; Bellini, G.; Giordano, M.E.; Rossi, F.; Scafuro, M.; Novellis, Vd.; Maione, S. Effects of a metabotropic glutamate receptor subtype 7 negative allosteric modulator in the periaqueductal grey on pain responses and rostral ventromedial medulla cell activity in rat. *Mol. Pain*, **2013**, *9*, 44-55. [http://dx.doi.org/10.1186/1744-8069-9-44] [PMID: 24004843]
- [107] Palazzo, E.; Romano, R.; Luongo, L.; Boccella, S.; De Gregorio, D.; Giordano, M.E.; Rossi, F.; Marabese, I.; Scafuro, M.A.; de Novellis, V.; Maione, S. MMPiP, an mGluR7-selective negative allosteric modulator, alleviates pain and normalizes affective and cognitive behavior in neuropathic mice. *Pain*, **2015**, *156*(6), 1060-1073. [PMID: 25760470]
- [108] Niswender, C.M.; Johnson, K.A.; Miller, N.R.; Ayala, J.E.; Luo, Q.; Williams, R.; Saleh, S.; Orton, D.; Weaver, C.D.; Conn, P.J. Context-dependent pharmacology exhibited by negative allosteric modulators of metabotropic glutamate receptor 7. *Mol. Pharmacol.*, **2010**, *77*(3), 459-468. [http://dx.doi.org/10.1124/mol.109.058768] [PMID: 20026717]
- [109] Kalinichev, M.; Rouillier, M.; Girard, F.; Royer-Urios, I.; Bournique, B.; Finn, T.; Charvin, D.; Campo, B.; Le Poul, E.; Mutel, V.; Poli, S.; Neale, S.A.; Salt, T.E.; Lütjens, R. ADX71743, a potent and selective negative allosteric modulator of metabotropic glutamate receptor 7: *in vitro* and *in vivo* characterization. *J. Pharmacol. Exp. Ther.*, **2013**, *344*(3), 624-636. [http://dx.doi.org/10.1124/jpet.112.200915] [PMID: 23257312]