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Behavioural profile of selective ligands for mGlu7 and mGlu8 glutamate receptors in agonistic encounters between mice

José Francisco Navarro, Vanessa de Castro and Mercedes Martín-López
Universidad de Málaga

Evidence is accumulating for a role of glutamate transmission in aggression modulation. Recent studies indicate that glutamate metabotropic receptors (mGlu1 and mGlu5) are involved in the regulation of aggressive behaviour. However, to date, the possible role of mGlu7 and mGlu8 receptors has not been explored. In this work, we analyze the effect of acute administration of AMN082 (0.5-4 mg/kg, ip) and (S)-3,4-DCPG (2.5-10 mg/kg, ip), selective ligands for the mGlu7 and mGlu8 receptors, respectively, on agonistic encounters between male mice. Individually housed mice were exposed to anosmic opponents 60 or 30 min after drug administration. Ten min of dyadic interactions were staged between a singly housed and an anosmic mouse in a neutral area. The encounters were videotaped and the accumulated time allocated by subjects to ten broad behavioural categories was estimated using an ethologically based analysis. The highest dose of AMN082 (4 mg/kg) significantly reduced offensive behaviours (threat and attack), as compared with the control group, without depressing motility, whereas (S)-3,4-DCPG did not produce significant behavioural changes. Overall, these results suggest that mGlu7 receptors (but not mGlu8) may be implicated in the modulation of aggression.

Perfil conductual de ligandos selectivos para los receptores de glutamato mGlu7 y mGlu8 en encuentros agonísticos entre ratones. Existe una evidencia creciente de la implicación del glutamato en la modulación de la agresión. Estudios recientes indican que los receptores metabotrópicos de glutamato (mGlu1 y mGlu5) están involucrados en la regulación de la conducta agresiva. Sin embargo, el posible papel de los receptores mGlu7 y mGlu8 no ha sido aún examinado. En este trabajo analizamos el efecto de la administración aguda de AMN082 (0.5-4 mg/kg) y (S)-3,4-DCPG (2.5-10 mg/kg), ligandos selectivos para los receptores mGlu7 y mGlu8, respectivamente, sobre los encuentros agonísticos entre ratones machos. Se llevaron a cabo interacciones agonísticas de 10 minutos de duración entre un animal aislado y un oponente anósmico en un área neutral, tras 60 y 30 minutos de la administración de ambos fármacos. Dichos encuentros fueron grabados en vídeo para su análisis etológico mediante un programa de ordenador, estimándose el tiempo pasado por los ratones en cada una de diez categorías conductuales. AMN082 (4 mg/kg) redujo significativamente las conductas ofensivas, sin disminuir la motilidad, en comparación con el grupo control, mientras que la administración de (S)-3,4-DCPG no produjo cambios conductuales significativos. Estos resultados sugieren que los receptores mGlu7 (pero no los mGlu8) podrían estar implicados en la modulación de la agresión.

Glutamate is the major excitatory neurotransmitter in the mammalian CNS, the actions of which are regulated by ionotropic glutamate (iGlu) and metabotropic glutamate receptors (mGlu). mGlu receptors are a family of G-protein-coupled receptors comprising eight members, refered to as mGlu1-8. Group I receptors include mGlu1 and mGlu5, which when expressed are coupled via Gq to phospholipase C. Group II (mGlu2 and mGlu3) and group III (mGlu4,6,7,8) receptors are coupled to Gi and inhibit cAMP formation when expressed in cell lines (Ferraguti & Shigemoto, 2006).

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Correspondencia: José Francisco Navarro
Facultad de Psicología
Universidad de Málaga
29071 Málaga (Spain)
E-mail: navahuma@uma.es

Glutamate is involved in the regulation of aggressive behaviour. In this sense, studies of ionotropic receptors (NMDA and AMPA) show that glutamate neurotransmission could play a role in aggression. In relation to the NMDA receptors, the existing results are equivocal. For instance, phencyclidine (PCP) was found both to facilitate fighting (Wilmot, Vanderwende, & Spoerlein, 1987) and to decrease the number of attacks by resident mice toward intruders (Miczek & Haney, 1994). Similarly, the PCP-like NMDA receptor antagonist dizocilpine increased aggressiveness in a study by McAllister (1990), whereas suppressed aggression induced by a challenge dose of apomorphine (Lang et al., 1995). By contrast, the involvement of AMPA-type glutamate receptors in the regulation of social behaviour has been clearly suggested by experiments with mice deficient for the GluR-A subunit-containing AMPA receptors showing reduced intermale aggression. Thus, of the AMPA family of glutamate receptors, knock-out mice lacking the

glutamate receptor 1 subunit (GluR1) exhibited notably reduced aggressive behavior in a variety of agonistic paradigms, indicating that signaling through glutamate receptors expressing this subunit may play an important role in aggression (Vekovischeva et al., 2004). Moreover, Vekovischeva et al. (2007) examined the effects of AMPA receptor antagonists (CNQX, NBQX, and GYKI 52466) on mouse social behavior towards unfamiliar Swiss–Webster males on a neutral territory were tested using male subjects from the Turku Aggressive (TA) and Turku Non-Aggressive (TNA) mouse lines bidirectionally selected for high and low levels of offensive aggression. In TA mice, CNQX and NBQX decreased the biting component of aggressive structure, while GYKI 52466 suppressed all aggressive manifestations, suggesting that AMPA receptors are involved in the modulation of aggression.

Furthermore, recent studies indicate that mGlu receptors (concretely, mGlu1 and mGlu5) are implicated in the regulation of aggressive behaviour. Thus, acute administration of MPEP (a selective antagonist of mGlu5 receptors) and JNJ16259685 (a selective antagonist of mGlu1 receptors), produced a robust reduction in offensive behaviours of mice, suggesting a role for these receptors in aggression modulation (Navarro, Postigo, Martín-López, & Burón, 2006; Navarro, De Castro, & Martín-López, 2008). Likewise, mGlu2/3 receptors also might be involved in aggressive behaviour (Navarro, Luque, De Castro, & Martín-López, 2008). However, to date the possible role of mGlu7 and mGlu8 receptors has not been examined. These receptors are presynaptic inhibitory autoreceptors that negatively modulate excitatory glutamate transmission. Recently, new positive and negative orthosteric or allosteric modulators for mGlu7 and mGlu8 receptors have been discovered allowing for pharmacological studies in animal models (Linden, Bergeron, Baez, & Schoepp, 2003; Mitsukawa et al., 2005). In this study, we analyze the effects of AMN082 (0.5-4 mg/kg, ip) and (S)-3,4-DCPG (2.5-10 mg/kg, ip), two selective ligands for the mGlu7 and mGlu8 receptors, respectively, on agonistic encounters between male mice using an animal model of isolation-induced aggression. Both drugs were chosen because they have been described as potent group III agonists that reduce excitatory transmission, and reach the brain at relevant concentrations after systemic administration (Linden et al., 2003; Mitsukawa et al., 2005).

A manipulation often used to induce aggression is isolation of male animals, typically mice, for several weeks. Many such isolated animals, on encountering another male, will reliably exhibit attack behavior. This isolation induced aggression paradigm in mice is one of the most frequently used aggression models in behavioural pharmacology. In socially cohesive species such as rats and most primate species, social isolation is stressful, whereas in mice and other rodents that disperse after puberty, single housing corresponds to the life of territorial males (Brain, 1975; Miczek, Yap, & Covington, 2008). Because isolated male mice show a full repertoire of agonistic behaviours, ethologic techniques have been used to detect very specific drug effects. The term agonistic behaviour encompasses flight and other actions that are threatening, aggressive, defensive, and submissive. The ethological analysis of these social encounters seems to be an appropriate technique for distinguishing between specific and non-specific drug-induced changes (Oliver & Van Dalen, 1982).

Methods

Animals

A total of 272 albino male mice of the OF.1 strain weighing 25-30 g were used. Animals were housed under standardized lighting conditions (white lights on: 20:00-08:00) at a constant temperature (21 ºC) with food and tap water available *ad libitum* except during behavioural trials. Upon arrival in the laboratory, mice were allocated to two categories. Half were housed individually in transparent plastic cages (24 × 13.5 × 13 cm) to be used as experimental animals. All experimental subjects were isolated for 30 days prior to behavioural testing since this housing is an effective means of increasing the level of aggressiveness, particularly in laboratory mice (Navarro, 1997). The remainder were housed in groups of five to be used as «standard opponents». These animals were rendered temporally anosmic by intranasal lavage with 4% zinc sulphate solution (Sigma Laboratories) on both days 1 and 3 before testing. This type of opponent elicits attack but never initiates such behaviour (Brain, Benton, Childs, & Parmigiani, 1981). Consequently, fighting is always unidirectional, and easily quantified.

Drug administration

In the Experiment 1, five groups of mice were used. Animals were randomly allocated to one control group (n= 19 each) receiving a vehicle of saline (90%) plus DMSO (10%), and four experimental groups (N= 15-16 each) receiving AMN082 injections. AMN082 (Tocris Laboratories) was diluted in saline (90%) plus DMSO (10%) to provide appropriate doses for injections and administered in four doses: 0.5, 1, 2 and 4 mg/kg. On the other hand, in the Experiment 2, four groups of mice were used, being mice randomly allocated to one control group (n= 14), receiving physiological saline, and three experimental groups (N= 13-14 each) receiving (S)-3,4-DCPG injections (Tocris Laboratories) in three doses: 2.5, 5 and 10 mg/kg. The doses (and the interval between injection and behavioural test) were chosen on the basis of previous pilot studies carried out in our laboratory and from recent behavioural studies using these compounds in rodents with a similar dose range to that employed in our experiments (Bäckström & Hyytiä, 2005; Palucha, Klak, Branski, van der Putten, Flor, & Pilc, 2007). Drug or vehicle was injected intraperitoneally in a volume of 10 ml/kg.

Behavioural test

60 (Experiment 1) or 30 (Experiment 2) minutes after injection, an isolated animal and a «standard opponent» were allowed to confront each other in a neutral area for 10 min. This neutral cage consisted of an all-glass arena, measuring 50 × 26 × 30 cm with a fresh sawdust substrate. Before the encounter, the animals were allowed 1 min of adaptation to the neutral cage, whilst separated by means of a plastic barrier. The social encounters were videotaped using a Sony-V8 camera. All tests were conducted under red light between the second and seventh hours of the dark phase of the lighting condition. After each encounter, the neutral cage was washed and the sawdust bedding was replaced. The tapes were analyzed using a microprocessor and a custom-developed program (Brain, McAllister, & Walmsey, 1989), which facilitated

estimating time and frequency allocated to ten broad behavioural categories. Only the behaviour of the isolated animal was assessed and the analysis was carried out by a trained experimenter 'blind' to the treatment administered to the experimental subjects. The categories and their constituent elements were as follows: (i) body care (including groom, self-groom, wash, shake, scratch); (ii) digging (dig, kick dig, push dig); (iii) non-social exploration (explore, rear, supported rear, scan); (iv) exploration from a distance (approach, attend, circle, head orient, stretched attention); (v) social investigation (crawl over, crawl under, follow, groom, head groom, investigate, nose sniff, sniff, push past, walk around); (vi) threat (aggressive groom, sideways offensive, upright offensive, tail rattle); (vii) attack (charge, lunge, attack, chase); (viii) avoidance/flee (evade, flinch, retreat, ricochet, wheel, startle, jump, leave, wall, clutch); (ix) defence/submission (upright defensive, upright submissive, sideways defensive), and (x) immobility (squat, cringe). This ethoexperimental procedure allows a complete quantification of the behavioural elements shown by the subject during the agonistic encounters (Brain et al., 1989).

Data analysis

The medians for times allocated to each behavioural category were determined. Non-parametric Kruskal-Wallis tests were used to assess the variance of the behavioural measures in the different treatment groups. Subsequently, appropriate paired comparisons were carried out using Mann-Whitney U-tests to contrast behaviours in different treatment groups. The analysis was performed using non-parametric statistics, since criteria for parametric statistics were not met by the data.

This experiment was carried out in accordance with the guiding principles for care and use of Laboratory Animals approved by the European Communities Council Directive of November 24, 1986 (86/609/EEC).

Results

The effects of acute administration of AMN082 and (S)-3,4-DCPG on agonistic interactions between male mice are shown in table 1 and 2, respectively (medians with ranges). In the Experiment 1, Kruskall-Wallis analysis showed that there was significant variance in the categories of body care ($p<0.06$), digging ($p<0.01$), nonsocial exploration ($p<0.0001$), exploration from a distance ($p<0.03$), threat ($p<0.0001$) and attack ($p<0.0001$). Paired comparisons using Mann-Whitney U-tests revealed that AMN082 (4 mg/kg) significantly reduced the time spent in body care ($p<0.001$), digging ($p<0.002$), threat ($p<0.0001$) and attack ($p<0.0001$), as compared with the vehicle group, whereas nonsocial exploration ($p<0.0001$) and exploration from a distance ($p<0.002$) behaviours were significantly increased. The median values for the categories of avoidance/flee, defence/submission and immobility were zero for all groups. In the Experiment 2, no significant differences were found between control and experimental groups in any in the behavioural categories analyzed.

Table 1
Medians values (with ranges) for times (sec) allocated to broad behavioural categories in animals receiving AMN082 (0.5, 1, 2 and 4 mg/kg)

Behavioural categories		**Doses of AMN082 (mg/kg)**			
Parameters	**Vehicle**	**0.5**	**1**	**2**	**4**
Body care[a]	9.41 (0-27)	9.8 (1-31)	6.6 (2-18)	5.4 (0-22)	1 ** (0-18)
Digging[c]	2.37 (0-30)	0.4 (0-23)	1.4 (0-26)	0.4 (0-27)	0 *** (0-5)
Non-social exploration[d]	371 (238-495)	345 (249-413)	378 (282-466)	381 (273-532)	476 * (421-531)
Exploration from a distance[b]	14.7 (0-27)	12.5 (0-45)	12.4 (2-50)	12.8 (1.5-32)	26.9 *** (4-66)
Social investigation	99 (8-175)	61.6 (3-202)	85.7 (0-272)	102 (4-270)	97 (38-149)
Threat[d]	92.5 (0-182)	149 (0-243)	99 (0-213)	27 (0-185)	0 * (0-2.4)
Attack[d]	6.6 (0-93)	11.4 (0-50)	8.1 (0-44)	2.4 (0-62)	0 * (0-0)
Avoidance/flee	0 (0-1.2)	0 (0-2.4)	0 (0-5)	0 (0-0)	0 (0-2)
Defence/submission	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-2)	0 (0-0)
Immobility	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)

Kruskal-Wallis test showed significant variance: [a]$p<0.006$; [b]$p<0.03$; [c]$p<0.01$; [d]$p<0.0001$
Differs from vehicle on Mann-Whitney U-tests: * $p<0.0001$; **$p<0.001$; ***$p<0.002$

Table 2
Medians values (with ranges) for times (sec) allocated to broad behavioural categories in animals receiving (S)-3,4-DCPG (2.5, 5 and 10 mg/kg)

Behavioural categories		**Doses of (S)-3,4-DCPG (mg/kg)**		
Parameters	**Vehicle**	**2.5**	**5**	**10**
Body care	8.9 (0-22)	11.3 (0.7-21)	11.4 (2-23)	9.7 (5-20)
Digging	13 (1-56)	17 (0.7-52.5)	12.4 (0-44.6)	12.5 (0-64.5)
Non-social exploration	376 (241-484)	343 (259-478)	367 (238-443)	373 (326-498)
Exploration from a distance	14.3 (2.3-52)	17.4 (4-44.7)	22.1 (5.7-82)	18.6 (3.5-53)
Social investigation	76.6 (2-125)	32.4 (10.4-313)	71 (2.6-196)	39.1 (5-148)
Threat	89.8 (0-289)	96.7 (0-224)	83.5 (3.7-296)	122 (0-188)
Attack	6.6 (0-34)	12.3 (0-53.6)	9.8 (0-45.2)	19.7 (0-56.4)
Avoidance/flee	0 (0-21)	0 (0-5)	0 (0-1.3)	0 (0-1)
Defence/submission	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Immobility	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-36.5)

No significant differences were found in any of the behavioural categories analysed

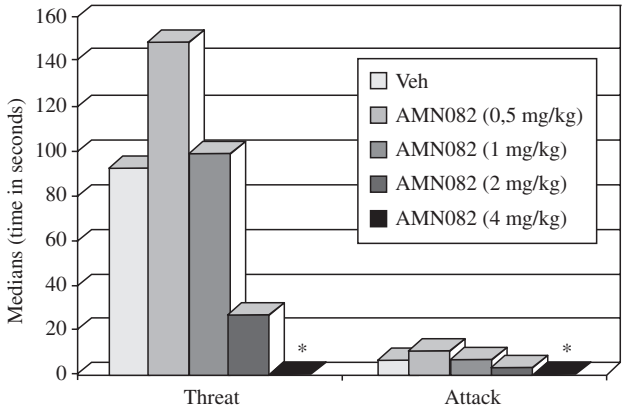

Figure 1. *Mann-Whitney U-tests (differs from vehicle): *p<0.0001*

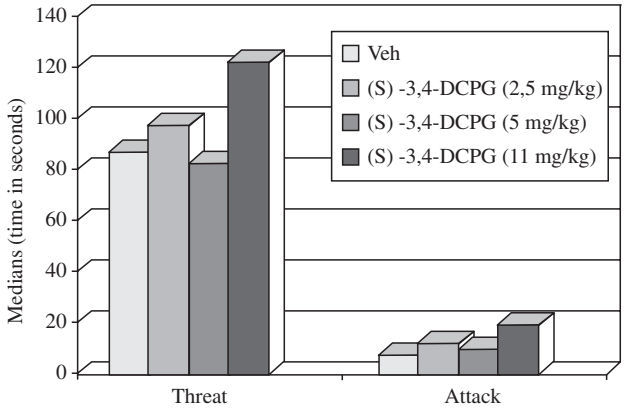

Figure 2

Discussion

mGlu7 and 8 glutamate receptors are implicated in numerous functions of the mammalian central nervous system. Thus, AMN082 (a selective ligand for mGlu7 receptors) induces specific behavioural effects in rodents, including an antidepressant action (Palucha et al., 2007), a blockade of the acquisition of conditioned fear (Siegl, Flor, & Fendt, 2008) as well as pro-nociceptive (Palazzo, Fu, Ji, Maione, & Neugebauer, 2008). In relation to anxiety, however, controversial data have been obtained for the mGlu7 receptors, with anxiolytic (Stachowicz et al., 2008) or anxiogenic (Palazzo et al., 2008) effects after AMN082 administration (Lavreysen & Dautzenberg, 2008). Furthermore, using (S)-3,4-DCPG and other ligands for mGlu8 receptors it has been suggested a potential role for these receptors in anxiety (Duvoisin et al., 2005; Linden et al., 2003), alcohol-seeking and self-administration (Bäckström & Hyytiä, 2005) and in modulating pain perception of mice (Marabese et al., 2007).

Pharmacological studies of group III mGlu receptors have been limited because subtype-selective and centrally bioavailable pharmacological tools are almost completely lacking. Recently, however, selective and systemically active agonists of mGlu7 (AMN082) and mGlu8 ((S)-3,4-DCPG) receptors, have been characterized (Linden et al., 2003; Mitsukawa et al., 2005). Both receptors are primarily localized presynaptically and are thought to function as autoreceptors. These receptors are a member of the group III mGluR and are widely distributed throughout the central nervous system. Mammalian brain is abundant in mGlu7 receptors which are highly expressed in most brain areas, including neocortical regions, cingulate and piriform cortices, CA1, CA3 and DG regions of hippocampus, amygdala, locus coeruleus, hypothalamic and thalamic nuclei (Ohishi, Akazawa, Shigemoto, Nakanishi, & Mizuno,1995). Expression of mGlu8 receptors appears to be dominant in presynaptic terminals in the olfactory bulbs, piriform cortex, entorhinal cortex, hippocampus, and cerebellum (Shigemoto et al., 1997). As Table 1 shows, acute administration of AMN082 (4 mg/kg) produced a significant reduction of offensive behaviours (threat and attack), without affecting immobility, as compared with vehicle group. This reduction of aggression was accompanied by a significant decrease of digging and body care behaviours. Digging is involved in aggressive behaviour together with the threats and attacking behaviour. In fact, there is usually a correlation between these behavioural domains (Kudryavtseva, Bondar, & Alekseyenko, 2000). Body care, an ethological response that is considered to be an important part of animal repertoire as it is sensitive to both endogenous and exogenous factors being useful in the assessment of behavioural reactivity to novelty and stress (Gómez, Carrasco, & Redolat, 2008), was also significantly decreased, an effect which has been described in association to a reduction of offensive behaviours (Navarro, De Castro, & Martín-López, 2008). Likewise, exploration from a distance (a behaviour which anticipates social contact) and nonsocial exploration behaviours were increased after AMN082 administration (4 mg/kg). By contrast, the acute administration of (S)-3,4-DCPG (2.5-10 mg/kg, ip), a selective ligand for mGlu8 receptors, did not modify any of the behavioural categories examined (see Table 2). The different implication of both mGlu7 and 8 receptors in modulation aggression could be related to the different brain distribution of these receptors in structures such as amygdala or hypothalamus.

This study is the first to investigate the role of mGlu7 and mGlu8 receptors in the regulation of aggression. It is concluded that mGlu7 receptors (but not mGlu8) might be implicated in the modulation of aggression. Additional experiments using other selective ligands for mGlu7 and 8 are needed to confirm these results.

References

Bäckström, P., & Hyytiä, P. (2005). Suppression 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. *European Journal of Pharmacology*, *528*, 110-118.

Brain, P.F. (1975). What does individual housing mean to a mouse? *Life Sciences*, *16,* 187-200.

Brain, P.F., McAllister, K.H., & Walmsey, S. (1989). Drug effects on social behaviour: Methods in ethopharmacology. In Boulton, A.A., Baker,

G.B., & Greenshaws, A.J. (Eds.): *Neuromethods.* Humana Press, New Jersey, 687-739.

Brain, P.F., Benton, D., Childs, G., & Parmigiani, S. (1981). The effects of the type of opponent in test of murine aggression. *Behavioral Processess*, *6*, 319-327.

Duvoisin, R.M., Zhang, C., Pfankuch, T.F., O'Connor, H., Gayet-Primo, J., Quraishi, S., & Raber, J. (2005). Increased measures of anxiety and weight gain in mice lacking the group III metabotropic glutamate receptor mGluR8. *European Journal of Neurosience*, *22*, 425-436.

Ferraguti, F., & Shigemoto, R. (2006). Metabotropic glutamate receptors. *Cell and Tissue Research*, *326,* 484-504.

Gómez, M.C., Carrasco, M.C., & Redolat, R. (2008). Differential sensitivity to the effects of nicotine and bupropion in adolescent and adult male OF1 mice during social interaction tests. *Aggressive Behavior, 34*, 369-379.

Kudryavtseva, N.N., Bondar, N.P., & Alekseyenko, O.V. (2000). Behavioral correlates of learned aggression in male mice. *Aggressive Behavior*, *26*, 386-400.

Lang, A., Harro, J., Soosaar, A., Koks, S., Volke, V., Oreland, L., Bourin, M., Vasar, E., Bradwejn, J., & Männistö, P.T. (1995). Role of N-methyl-D-aspartic acid and cholecystokinin receptors in apomorphine-induced aggressive behaviour in rats. *Naunyn-Schmiedeberg's archives of Pharmacology*, *351*, 363-370.

Lavreysen, H., & Dautzenberg, F.M. (2008). Therapeutic potential of group III metabotropic glutamate receptors. *Current Medicinal Chemistry*, *15*, 671-684.

Linden, A.M., Bergeron, M., Baez, M., & Schoepp, D.D. (2003). Systemic administration of the potent mGlu8 receptor agonist (S)-3,4-DCPG induces c-Fos in stress-related brain regions in wild-type, but not mGlu8 receptor knockout mice. *Neuropharmacology*, *45*, 473-483.

Marabese, I., Rossi, F., Palazzo, E., de Novellis, V., Starowicz, K., Cristino, L., Vita, D., Gatta, L., Guida, F., Di Marzo, V., Rossi, F., & Maione, S. (2007). Periaqueductal gray metabotropic glutamate receptor subtype 7 and 8 mediate opposite effects on amino acid release, rostral ventromedial medulla cell activities, and thermal nociception. *Journal of Neurophysiology*, *98*, 43-53.

McAllister, K.H. (1990). Ethological analysis of the effect of MK-801 upon aggressive male mice: similarity to chlordiazepoxide. *Pharmacology Biochemistry and Behavior*, *37*, 101-106.

Miczek, K.A., & Haney, M. (1994). Psychomotor stimulant effects of d-amphetamine, MDMA and PCP: Aggressive and schedule-controlled behavior in mice. *Psychopharmacology*, *115*, 358-365.

Miczek, K.A., Yap, J.J., & Covington III, H.E. (2008). Social stress, therapeutics and drug abuse: Preclinical models of escalated and depressed intake. *Pharmacology & Therapeutics*, *120,* 102-128.

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. (2005). A selective metabotropic glutamate receptor 7 agonist: Activation of receptor signaling via an allosteric site modulates stress parameters in vivo. *Proceedings of the National Academy of Sciences USA*, *102*, 18712-18717.

Navarro, J.F. (1997). An ethoexperimental analysis of the agonistic interactions in isolated male mice: Comparison between OF.1 and NMRI strains. *Psicothema*, *9*, 333-336.

Navarro, J.F., Postigo, D., Martín-López, M., & Burón, E. (2006). Antiaggressive effects of MPEP, a selective antagonist of mGlu5 receptor, in agonistic interactions between male mice. *European Journal of Pharmacology*, *551*, 67-70.

Navarro, J.F., De Castro, V., & Martín-López, M. (2008). JNJ16259685, a selective mGlu1 antagonist, suppresses isolation-induced aggression in male mice. *European Journal of Pharmacology*, *586*, 217-220.

Navarro, J.F., Luque, M.J., De Castro, V., & Martín-López, M. (2008). Effects of LY379268, a selective agonist of mGlu2/3 receptors, on isolation-induced aggression in male mice. *European Neuropsychopharmacology*, *18* (suppl. 4), S252.

Ohishi, H., Akazawa, C., Shigemoto, R., Nakanishi, S., & Mizuno, N. (1995). Distributions of the mRNAs for L-2-amino-4-phosphonobutyrate-sensitive metabotropic glutamate receptors, mGluR4 and mGluR7, in the rat brain. *Journal of Comparative Neurology*, *360*, 555-570.

Oliver, B., & Van Dalen, D. (1982). Social behaviour in rats and mice: An ethologically based model for differentiating psychoactive drugs. *Aggressive Behavior*, *8*, 163-168.

Palazzo, E., Fu, Y., Ji, G., Maione, S., & Neugebauer, V. (2008). Group III mGluR7 and mGluR8 in the amygdala differentially modulate nocifensive and affective pain behaviors. *Neuropharmacology*, *55*, 537-545.

Palucha, A., Klak, K., Branski, P., van der Putten H., Flor, P.J., & Pilc, A. (2007). Activation of the mGlu7 receptor elicits antidepressant-like effects in mice. *Psychopharmacology*, *194*, 555-562.

Shigemoto, R., Kinoshita, A., Wada, E., Nomura, S., Ohishi, H., Takada, M., Flor, P.J., Neki, A., Abe, T., Nakanishi, S., & Mizuno, N. (1997). Differential presynaptic localization of metabotropic glutamate receptor subtypes in the rat hippocampus. *Journal of Neuroscience*, *17*, 7503-7522.

Siegl, S., Flor, P.J., & Fendt, M. (2008). Amygdaloid metabotropic glutamate receptor subtype 7 is involved in the acquisition of conditioned fear. *Neuroreport*, *19*, 1147-1150.

Stachowicz, K., Brañski, P., Klak, K., van der Putten, H., Cryan, J.F., Flor, P.J., & Andrzej, P. (2008). Selective activation of metabotropic G-protein-coupled glutamate 7 receptor elicits anxiolytic-like effects in mice by modulating GABAergic neurotransmission. *Behavioural Pharmacology*, *19*, 597-603.

Vekovischeva, O.Y., Aitta-Aho, T., Echenko, O., Kankaampää, A., Seppäla, T., Honkanen, A., Sprengel, R., & Korpi, E.R. (2004). Reduced aggression in AMPA-type glutamate receptor GluR-A subunit-deficient mice. *Genes Brain and Behavior*, *3*, 253-265.

Vekovischeva, O.Y., Aitta-aho, T., Verbitskaya, E., Sandnabba, K., & Korpi, E.R. (2007). Acute effects of AMPA-type glutamate receptor antagonists on intermale social behavior in two mouse lines bidirectionally selected for offensive aggression. *Pharmacology Biochemistry and Behavior*, *87*, 241-249.

Wilmot, C.A., Vanderwende, C., & Spoerlein, M.T. (1987). The effects of phencyclidine on fighting differentially housed mice. *Pharmacology Biochemistry and Behavior*, *28*, 341-346.