Available online at www.sciencedirect.com
ScienceDirect
Pharmacology, Biochemistry and Behavior 87 (2007) 241 – 249
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Acute effects of AMPA-type glutamate receptor antagonists on intermale social behavior in two mouse lines bidirectionally selected for offensive aggression

O.Yu. Vekovischeva [a,*], T. Aitta-aho [a], E. Verbitskaya [b], K. Sandnabba [c], E.R. Korpi [a]

[a] *Institute of Biomedicine/Pharmacology, Biomedicum Helsinki, P.O. Box 63 (Haartmaninkatu 8), FIN-00014 University of Helsinki, Finland*
[b] *Laboratory of Biomedical Statistics, Pavlov State Medical University, Lev Tolstoy str., 6/8, 197089, St. Petersburg, Russia*
[c] *Department of Psychology, Åbo Academi University, Turku, 20500, Finland*

Received 5 July 2006; received in revised form 1 March 2007; accepted 25 April 2007
Available online 1 May 2007

Abstract

Involvement of AMPA-type glutamate receptors in the regulation of social behavior has been suggested by experiments with mice deficient for the GluR-A subunit-containing AMPA receptors showing reduced intermale aggression. In the present study, effects of AMPA receptor antagonists 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. The drugs were the competitive antagonists 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) and 2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[f] quinoxaline-7-sulfonamide (NBQX), and the non-competitive antagonist 4-(8-methyl-9*H*-1,3-dioxolo[4,5-*h*][2,3]benzodiazepin-5-yl)-benzenamine (GYKI 52466). In TA mice, CNQX and NBQX decreased the biting component of aggressive structure, while GYKI 52466 suppressed all aggressive manifestations. All drugs increased anxiety-like behavior towards the partner. In TNA mice, NBQX activated mouse social behavior and ambivalent aggression, while CNQX and GYKI 52466 only increased anxiety. Thus, AMPA receptor antagonists affect aggressive behaviors in TA mice supporting the idea that AMPA receptors are involved in the modulation of agonistic impulsive behavioral pattern. GYKI 52466 appeared to be the most selective and efficacious in suppressing the aggression.

Keywords: AMPA receptor antagonists; CNQX; NBQX; GYKI 52466; Mouse; Aggression; Social behavior

1. Introduction

Aggression, as a multi-component behavioral pattern, accompanies many psychiatric disorders both as an emotional state and behavioral expression (Lopez et al., 2004). Genetically selected (Sluyter et al., 2003) or modified (Gingrich and Hen, 2001) animal models in combination with neurobiological analyses have clarified, at least partly, the mechanisms behind violent demeanors, as well as enabled preclinical testing of the efficacy of possible pharmacological treatments (Miczek et al., 2001; de Waal, 2004). The neural circuits for many types of human and animal aggression involve specific receptor subtypes of serotonin, dopamine and γ-aminobutyric acid transmitter systems (Miczek et al., 2002). The question whether the glutamate system, the main excitatory neurotransmitter system in the brain, participates in the regulation of aggressive behavior has, however, remained controversial (Siegel et al., 1999; Davidson et al., 2000). Regulation of aggression through L-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors was suggested in experiments with male mice deficient for the GluR-A subunit containing AMPA receptors (Vekovischeva et al., 2004), where knockout mice showed less aggressive behaviors than their wild-type littermates. GluR-A subunits are strongly expressed, e.g., in the cerebral cortex, amygdala and hippocampus (Keinanen et al., 1990). Since the GluR-A knockout mice have reduced AMPA receptor function at least in the hippocampus, amygdala and spinal cord (Zamanillo

* Corresponding author. Tel.: +358 9 191 25337; fax: +358 9 191 25364.
E-mail addresses: olga.vekovischeva@helsinki.fi (O.Yu. Vekovischeva), aittaaho@helsinki.fi (T. Aitta-aho), verboel@spmu.rssi.ru (E. Verbitskaya), ksandnab@abo.fi (K. Sandnabba), esa.korpi@helsinki.fi (E.R. Korpi).

0091-3057/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2007.04.020

et al., 1999), it can be hypothesized that general antagonism of AMPA receptors would result in reduced aggression. To test the effects of AMPA receptor antagonists on social behavior, animals from two mouse lines known to differ in aggression, were chosen: Turku Aggressive (TA) mice with their acute form of aggression towards an intruder were compared to Turku Non-Aggressive (TNA) mice that display hardly any agonistic behavior. These mouse lines have been bred by bidirectional selection for isolation-induced male offensive aggression and their main behavioral features are well defined (Lagerspetz and Lagerspetz, 1971; Sandnabba, 1996; Nyberg et al., 2004). They have extensively been used as a model for differences in innate aggression and aggression-related social behavior and consequently changes in their aggressive behavior should clearly reveal pharmacological efficacy of the AMPA receptor antagonists.

Due to the fact that there are no AMPA receptor subunit- or subtype-selective antagonists, three of the AMPA/kainate receptor antagonists were tested in the present study: the competitive antagonists 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) and 2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[*f*]quinoxaline-7-sulfonamide (NBQX), and the non-competitive antagonist 4-(8-methyl-9*H*-1,3-dioxolo[4,5-*h*][2,3]benzodiazepin-5-yl)-benzenamine (GYKI 52466). Effects of these drugs on aggressive behavior in mice have not been investigated earlier, but it has been found that they acutely affect spontaneous and drug-stimulated locomotor activity (Maj et al., 1995a,b), exploratory behavior (Czlonkowska et al., 1997) as well as anxiety (Karcz-Kubicha and Liljequist, 1995). All these findings suggest that the ligands could also affect aggression and aggression-related social behaviors. For that, adult TA and TNA male mice, individually housed since weaning, received acutely CNQX, NBQX or GYKI 52466 before an encounter with unfamiliar partner on a neutral territory. Behavioral elements were observed for 9 min and statistically analyzed using different statistical methods to get a comprehensive picture of the drug effects on aggression and aggression-related social behaviors.

2. Materials and methods

2.1. Subjects

TA and TNA mouse lines have been selected from an outbred colony of Swiss albino mice (in this study referred to as SW) in Turku, Finland. The breeding program for isolation-induced intermale offensive aggression started as early as 1959, and the selection has been performed in both directions of aggression display (Lagerspetz, 1964; Sandnabba, 1996). The approximately 3-month-old subjects used in the present study were male mice of the 75th generation of selection. Altogether 42 TA and the same number of TNA males were involved in the experiment. Group-housed SW males ($n=6$) of the same age were used as standard opponents.

Each mouse line was kept in separate air-conditioned room maintained at approximately 23 °C on 12-h day/night cycle with lights on at 07:00 h. After weaning at 21 days of age, the animals were housed individually in 22×17×14 cm clear polycarbonate cages with wire lids. The opponents from the SW line were housed in groups of six in 38×15×22 cm polycarbonate cages. Tap water and standard laboratory chow (Lab For) were available ad libitum. The ethical aspects of the research plan and experimental procedures had been approved by the Ethical Committee for Laboratory Animal Research at the Åbo Akademi University.

2.2. Behavioral testing

TA and TNA male individuals were subjected to 9-min encounters with an unfamiliar SW opponent on a neutral territory (a round glass arena: 18.5 cm in diameter and 11 cm high) without bedding 5–15 min after intraperitoneal injections of the drugs or saline. The arena was cleaned after each encounter. The tests were conducted between 09:00 and 13:00 h. All encounters were video-recorded and analyzed subsequently using a computer-assisted data acquisition system (Ethograph, 2.06, Ritec, St. Petersburg, Russia) (Poshivalov et al., 1988; Vekovischeva et al., 2004). Most of the behavioral elements were combined in seven main behavioral categories described in Table 1: *Consummate aggression* as a complete act of aggression, *Ambivalent aggression* as a demonstration of aggressive intentions, *Defense*, *Partner exploration*, *Non-aggressive contacts with partner*, *Locomotion* (all observed horizontal movements), and *Ambivalent stances*. Single behavioral elements, such as *Self-grooming*, *Rears*, and *Sitting with sniffing,* were analyzed separately, and together with *Other behaviors*, they were included in the analysis of pooled behavioral elements containing also the elements within the behavioral categories. Differentiation between the two behavioral elements "passive contact with partner "and "grouping together with partner" was based on which animal was the initiator of the physical contact. This distinction is important for further interpretation: in the case of "passive contact" the initiator was the partner, while in the case of "grouping together" it was the subject of the test. Some behavioral elements such as "tail rattling", "tremor" and "palpebral closure", were registered as secondary elements, in parallel with other elements.

2.3. Drugs and drug administration

CNQX as a disodium salt was tested at the doses of 0.75, 1.5 and 3.0 mg/kg, NBQX as a dosodium salt at the doses of 3.5, 7.0 and 10.0 mg/kg, and GYKI 52466 as a hydrochloride salt at the doses of 2.5 and 5.0 mg/kg. The drugs were dissolved into saline (0.9% NaCl) and injected intraperitoneally at the volume of 10 ml/kg body weight. Observation of the treatment and saline effects were commenced at 15 min after injections except for GYKI 52466, when observation was started at 5 min after injection, because it has a short half-live after systemic administration (Lees, 2000). The doses were selected so that they would not affect locomotor activity, on the basis of their neuropharmacological efficacy in rodents according to previous published studies (Karcz-Kubicha and Liljequist, 1995; Maj et al., 1995a,b; Czlonkowska et al., 1997; Stephens and Brown, 1999). All drugs were purchased from Tocris Cookson Ltd.,

Table 1
Total durations and relative frequencies of behavioral categories and related elements after saline treatment in TA and TNA mice

Behavior categories	Behavioral elements and their abbreviations		TA mice		TNA mice	
			Total duration	Relative frequency	Total duration	Relative frequency
Consummate aggression	Category		77±9#	0.04±0.05#	1.2±1.1	0.01±0.01
	Fighting	F	8.8±3.3#	0.05±0.02#	0±0	0±0
	Biting	B	48±7#	0.25±0.03#	1.2±1.1	0.01±0.01
	Boxing with partner	Bx	21±5#	0.13±0.03#	0±0	0±0
Ambivalent aggression	Category		137±14#	0.79±0.04#	2.6±1.9	0.03±0.02
	Rushing to attack	RshA	1.6±1.0#	0.01±0.01#	0±0	0±0
	Tail rattling‡	TlRt	60±8#	0.41±0.04	2.2±1.5	0.02±0.02
	Threat	Thr	54±7#	0.28±0.02#	0.42±0.42	0.01±0.01
	Circling around partner*	Cir	21±6#	0.09±0.02#	0±0	0±0
Defense	Category		15±6	0.07±0.03	11±4	0.06±0.02
	Kicking of partner	Kk	0.67±0.49	0.00±0.00	0.12±0.12	0.01±0.01
	Avoidance*	Av	10±3	0.05±0.02	0.47±0.26	0.01±0.00
	Posture on the back	Bk	0±0	0±0	0±0	0±0
	Evasion	Ev	3.0±2.1	0.01±0.01	1.9±0.9	0.02±0.01
	Freezing	Fz	1.1±0.7	0.01±0.00	8.9±3.2	0.03±0.01
Partner exploration	Category		119±17	0.59±0.07#	137±30	0.81±0.12
	Sniffing of partner's body	SnPr	69±10	0.35±0.04#	96±20	0.55±0.07
	Sniffing of partner's anogenital area	SxSnPr	43±9	0.22±0.04	24±7	0.17±0.05
	Grooming of partner	GrPr	6.6±3.8	0.02±0.01#	18±5	0.09±0.03
Ambivalent stances	Category		0.67±0.47	0.01±0.01	0±0	0±0
	Lateral stance	LS	0.20±0.15	0.01±0.01	0±0	0±0
	Vertical stance	VS	0.47±0.47	0.01±0.01	0±0	0±0
Locomotion*	Category		94±8#	0.55±0.03#	34±10	0.31±0.06
	Quick locomotion	QL	10±2#	0.07±0.02#	0.71±0.29	0.01±0.00
	Locomotion with sniffing	LSn	25±2	0.14±0.01	23±7	0.16±0.03
	Chasing	Ch	2.2±0.6	0.02±0.01	2.0±0.6	0.04±0.01
	Approach	App	26±3#	0.17±0.02#	7.3±2.9	0.09±0.04
Non-aggressive contacts with a partner	Category		26±9#	0.11±0.04#	94±15	0.51±0.07
	Climbing over	CIO	0.14±0.14	0.01±0.01	0±0	0±0
	Climbing under	CIU	3.7±1.9#	0.02±0.01	15±4	0.11±0.03
	Toss of partner	TPr	0.40±0.27	0.01±0.01	0.81±0.73	0.01±0.01
	Sexual contact with partner	SxPr	0±0	0±0	0±0	0±0
	Passive contact with partner	Pass	17±9	0.08±0.04#	42±11	0.25±0.05
	Grouping together with partner	Grp	4.3±2.7#	0.01±0.01#	36±12	0.14±0.04
Self-grooming		Gr	15±4	0.04±0.01	11±3	0.03±0.01
Rears		R	17±3	0.09±0.01	8.7±5.9	0.09±0.05
Sitting with sniffing		StSn	120±18	0.36±0.04#	176±26	0.62±0.06
Other behaviors	Rotation	rt	5.8±0.7#	0.05±0.01#	1.1±0.4	0.02±0.01
	Stretched attend posture	SAP	4.4±2.4#	0.02±0.01#	0±0	0±0
	Sitting	St	3.4±0.9	0.01±0.01	8.2±3.7	0.04±0.02
	Scratch	sc	0.15±0.87	0±0	0±0	0±0
	Tremor‡	tr	0.08±0.08	0±0	0±0	0±0
	Palpebral closure‡	plp	1.37±0.70	0.01±0.01#	15±9	0.08±0.03
	Shake	sh	0±0	0±0	0±0	0±0
	Jump	j	0±0	0±0	0±0	0±0
	Lying with sniffing	ln	0±0#	0±0#	50±21	0.12±0.05
	Lying prone	lnpr	0±0	0±0	0±0	0±0
	Feeding	fd	0±0	0±0	0±0	0±0

Total durations (seconds) and relative frequencies (number of events as a fraction of the number of all events) during 9-min periods 15 min after saline administration are presented as means±SEM ($n=9$). #$p<0.05$ for the significance of the difference from the corresponding values of the TNA mice (pairwise comparison by MANCOVA). *The elements were also included in Locomotion category; ‡the secondary elements which were registered in parallel with other primary elements. Registration of Pass or Grp was dependent on who, partner or subject, was the initiator of coming into contact.

Avonmouth, UK. All variants of drug dose were tested in parallel for TA-partner and TNA-partner pairs. Data were collected from several days.

To collect data of 9-member group for each dose-point, some animals received drug injections two or three times with 3–4 day washout periods. The animals, which received several injections in Latin square order, were treated first with saline or the smallest dose of the drugs to prevent any possible irreversible effects on the subjects by the highest doses. Since the influence of repeated treatment and different partner might significantly affect the behavior, the parameters were made as covariates in statistical analysis (see below).

2.4. Statistical analyses

The statistical significance of the drug-induced alterations in behavioral structure was conducted using SPSS software (release 12.0.1 for Windows). Drug-free behavioral differences between TA and TNA mice are well known (Nyberg et al., 2003, 2004), and were also confirmed in the present study (see Table 1).

The idea to split the 9-min observation period into three 3-min intervals emerged after pilot statistical analysis. Thus, time interval appeared significant for many behavioral measurements and the drugs were effective mostly during first 6 min, i.e., during the first and second time intervals (see Results). Moreover, drug effects in multivariate general linear procedure for the 9-min period were often insignificant, indicating loss of many findings when time interval was not taken into consideration.

The 3-min behavioral sequences and the behavioral categories as well as the separated behavioral elements (described above) were analyzed by MANCOVA, which made it possible to rule out possible effects of imbalanced factors such as a Partner and Order of the test. These imbalance factors were introduced as covariates to equalize their possible impact for all animals. Doses (4 levels for CNQX and NBQX and 3 levels for GYKI 52466) and Time intervals (3 levels for all drugs) were included in the analysis as principal factors. The multivariate criterion Wilks' Lambda (WL) was used to determine the significant effects on the behavior. Each behavioral measurement such as *total duration* (TD) — absolute duration of the behavioral element, *total frequency* (TF) — number of behavioral elements, and *relative frequency* (RF) — the proportion of the total frequency of an element of the sum of total frequencies of all elements, were analyzed separately. Statistical analysis of the pools of separated behavioral elements and behavioral categories was done independently also. Bonferroni post-hoc test was conducted for pairwise between-group comparisons if MANCOVA revealed significant main effects (null hypothesis was rejected at the $p<0.05$ level).

Traditional statistical approach was supplemented by discriminant function analysis, a multivariate statistical technique which is typically used: 1) to distinguish between predefined groups on the basis of differences in multiple measurements, 2) to identify the variables which contribute significantly to group differences and, thus best predict group membership, 3) to determine an optimal manner for distinguishing between groups, and 4) to determine group membership of the unclassified individuals (Leighty et al., 2004). We used SPSS classification discriminant procedure based on Mahalanobis distance. Mahalanobis distance is a measure of how much a case's values on independent variables differ from the average values of all cases. A large Mahalanobis distance identifies a case as having extreme values on one or more of the independent variables. We used "Stepwise-Forward" procedure that generates a mathematical model which incorporates specific variables chosen by iterative selection and testing. This procedure begins with no variables in the model, then constructs a model by including (or removing sometimes) variables one by one until all variables are examined, while conducting significance test at each step. The discriminant analysis was done for the pooled values of TD, TF or RF measurements for all behavioral elements during the 9-min observation periods.

3. Results

3.1. Behavior of the mouse lines after saline administration

The behavioral structures of the TA and TNA mice after saline are presented in Table 1 as TD and RF measurements for the whole 9-min observation period. Consummate and Ambivalent aggressions were important elements of TA behavioral structure and they were almost absent in TNA mice. Also longer duration and more frequent locomotory events were observed in the TA mice. On the other hand, the TNA mice exhibited more Partner exploration and Non-aggressive contacts with partners. All the mouse line differences prevailed also in the analysis of 3-min periods.

Although the partners were exchanged and some of the TA and TNA animals were tested repeatedly, both the factors Partner and Order of test did not have an effect on the saline- and drug-related behaviors (TA mice: WL=1.264, $p=0.356$ and WL=0.772, $p=0.716$; TNA mice: WL=1.093, $p=0.486$ and WL=2.188, $p=0.147$, for Partner and Order of test, respectively).

Discrimination analysis of behavioral structures of TA and TNA mice after saline administration built on TD, TF and RF of the behavioral elements was able to correctly classify 100% of original grouped cases and 100% of cross-validated cases. The principal elements of the discrimination appeared "tail rattling" (TD and RF), "chasing" (TD and RF), "boxing" (RF), "avoidance" (TD), "grouping together with partner" (RF), "biting" (RF), "toss of partner" (RF) and "freezing" (TD).

3.2. Effects of AMPA receptor antagonists

Table 2 gives an overview of the effects of CNQX, NBQX and GYKI 52466 on the behavioral structure of TA and TNA mice. It depicts the significant changes after drug administration at any of the 3-min periods analyzed. This summary indicates that the mouse lines were differentially affected by different AMPA antagonists. Most importantly, Consummate aggression was reduced in the TA mice, categorically especially by GYKI 52466, although "biting" was reduced by all drugs. GYKI 52466 elevated Defense, Ambivalent stances and Non-aggressive contacts in the TA mice, while also other AMPA antagonist appeared efficient in elevating these behaviors in the TNA mice. Below, this overall analysis is extended to more detailed inspection of the drug effects in various 3-min periods on the TA and TNA mice separately.

3.3. Effects of CNQX

3.3.1. TA mice

As compared to the saline treatment, CNQX affected total durations (TD) of pooled behavioral elements in the TA mice (WL=2.04, $p=0.006$). Although the time interval appeared insignificant ($p=0.127$), the drug×time interval interaction appeared significant (WL=1.57, $p=0.009$). Thus, "climbing

Table 2
The significant alterations of behavioral categories induced by AMPA antagonists in TA and TNA mice

Behavior categories	Behavioral elements	TA mice		TNA mice	
		Total duration	Relative frequency	Total duration	Relative frequency
Consummate aggression	Category	↓b, c	↓c		
	B	↓a, b, c	↓a, b, c		
	Bx	↓c	↓c		
Ambivalent aggression	Category			↑b	↑b
	RshA		↓a, b		
	TlRt			↑b	↑b
	Thr				↑b
Defense	Category	↑c	↑c	↑a	↑c
	Fz	↑a	↑c	↑a	
Partner exploration	Category	↓b		↓c	↓c
	SnPr	↓b			
	SxSnPr		↓c		
	GrPr	↑b	↑b, c		↓b
Ambivalent stances	Category	↑c	↑c	↑a, c	↑a, b, c
	LS	↑c	↑c	↑a	↑a
	VS	↑c		↑a	↑a, b
Locomotion	Category				
	QL		↓a		
	Ch		↑c		
Non-aggressive contacts with a partner	Category	↑c	↑c	↑b	↑a
	CIO	↑a			↑b
	CIU		↑c		
	SxPr		↑b		
	Pass			↑b	
	Grp	↑c	↑c		
Self-grooming	Gr		↑c		
Rears	R	↑b			
Other behaviors	rt			↑a	
	SAP	↑a	↑a, c	↑a	
	plp				↓a
	ln	↑c			
	lnpr			↑b	↑b

↑ or ↓ significant ($p<0.05$) increase or decrease of the whole behavioral category or its elements by CNQX (a), NBQX (b) and GYKI 52466 (c). For the abbreviations of behavioral elements, please see Table 1.

over" increased at the dose of 0.75 mg/kg on the second time interval and at 1.5 and 3 mg/kg on the third time interval ($F_{6,107}=21.61$, $p=0.0001$). "Stretched attend posture" increased at 0.75 mg/kg on the second and third time intervals ($p=0.03$). "Freezing" increased at 1.5 mg/kg on the second time interval and at 3 mg/kg on the first time interval ($p=0.006$). "Biting" depended on the dose only and was significantly decreased at the doses of 0.75 and 1.5 mg/kg ($p=0.004$). "Chasing" tended to increase by the dose of 1.5 mg/kg ($p=0.047$).

CNQX did not affect the total frequency (TF) of all behavioral elements or behavioral categories at any time interval (WL<1.483, $p\geq0.08$). However, the relative frequencies (RF) of behavioral elements depended on the drug dose (WL=1.59, $p=0.045$), but not on time interval ($p=0.072$). RFs of "rushing to the attack" and "quickly locomotion" were decreased by all CNQX doses ($F_{3,107}\geq6.65$, $p\leq0.002$), and that of "biting" decreased at the dose of 0.75 mg/kg ($p=0.017$). "Stretched attend posture" increased at the dose of 0.75 mg/kg ($p=0.001$).

3.3.2. TNA mice

CNQX also affected the TDs of TNA mouse behavioral categories (WL=4.13, $p=0.0001$), while there was no significant time interval effect or interaction (WL≤1.6, $p\geq0.06$). Ambivalent stances increased ($F_{3,107}=7.47$, $p=0.0001$) at 0.75 mg/kg due to increased "lateral stances" and "vertical stances" ($p\leq0.031$). Defense increased at 3.0 mg/kg due to increased "freezing" ($p=0.0001$). "Rotation" and "Stretched attend posture" increased ($p\leq0.013$) at the dose of 1.5 mg/kg.

CNQX also affected the TF of behavioral categories in the TNA mice (WL=2.7, $p=0.0001$) and the time interval was also significant (WL=1.88, $p=0.03$). However, only one alteration was found: Ambivalent stances increased by the doses of 0.75 and 3.0 mg/kg at first time interval ($F_{3,107}=10.3$, $p=0.0001$). Analysis of RFs of the behavioral categories identified significant drug (WL=4.26, $p=0.0001$) and time interval effects ($p=0.0001$) as well as the interaction of both factors ($p=0.0001$). Non-aggressive contacts with a partner increased at the dose of 3.0 mg/kg on the second interval ($F_{3,107}=5.52$, $p=0.02$). Ambivalent stances increased at 0.75 and 3 mg/kg on the first time interval ($F_{3,107}=25.54$, $p=0.0001$) due to increased "lateral stances" and "vertical stances" ($p\leq0.0001$). "Palpebral closure" decreased at 0.75 mg/kg ($p=0.021$).

3.4. Effects of NBQX

3.4.1. TA mice

Analysis of the TDs of the behavioral categories revealed significant drug dose and time interval effects in the behavioral actions of NBQX in the TA mice (WL=1.8, $p=0.03$ and WL=2.35, $p=0.01$, respectively), but no significant interaction (WL=0.369, $p=1.0$). There was an interaction for the pooled behavioral elements (WD=4.306, $p=0.0001$). Consummate aggression was decreased by all doses ($F_{3,107}=3.81$, $p=0.017$) on the third time interval due to decreased "biting" ($p=0.006$). Partner exploration decreased at 10 mg/kg on the second and third time intervals ($p=0.001$) due to decreased "sniffing of partner's body" ($p=0.008$), while "grooming of partner" increased at 3.5 mg/kg on the first and second time intervals ($p=0.0001$). "Rears" increased at the dose of 7.0 mg/kg ($p=0.0001$) on all time intervals.

NBQX doses or time intervals did not affect TFs of pooled behavioral elements or behavioral categories (WL≤1.76, $p\geq0.06$). Analysis of RFs of the pooled behavioral elements identified a significant drug effect (WL=3.69, $p=0.001$), but no time interval effect ($p=0.57$). RFs of the behavioral categories did not depend on the factors (WL=1.51, $p=0.09$ and WL=1.78, $p=0.06$, respectively, for dose and time interval effects). RF of "biting" decreased at 3.5 ($F_{3,107}=3.68$, $p=0.02$), and "rushing to attack" at 3.5 and 10.0 mg/kg ($p=0.006$). "Grooming of partner" and "sexual contact with partner" increased at 3.5 mg/kg ($p=0.0001$ for both).

3.4.2. TNA mice

Analysis of TDs of the behavioral categories indicated a significant NBQX effect (WL=3.17, $p=0.001$), but no time interval effect or interaction ($p\geq0.33$). Ambivalent aggression

increased ($F_{3,107}$=8.15, p=0.0001) at the dose of 3.5 mg/kg mainly because of increased "tail rattling" (p=0.0001). Non-aggressive contacts with partner increased (p=0.001) at 7 mg/kg due to "passive contact with partner" (p=0.009). "Lying prone" was increased by the doses of 3.5 and 7 mg/kg (p=0.0001).

Analysis of TFs of the behavioral categories revealed a significant drug effect (WL=5.57, p=0.001), but no time interval effect (p=0.21) or interaction (p=0.46). Time interval effect and drug×time interaction for TFs of the pooled behavioral elements were significant (WL=1.97, p=0.04 and WL=1.72, p=0.004, respectively) as well as drug effect (WL=8.18, p=0.0001). Ambivalent aggression increased ($F_{3,107}$=16.84, p=0.0001) at the dose of 3.5 mg/kg due to "tail rattling" (p=0.0001) and "threat" (p=0.0001). Ambivalent stances increased (p=0.001) at 10.0 mg/kg due to increased "vertical stances" (p=0.0001). Changes in Non-aggressive contacts with a partner (p=0.003) might have been related to increased "climbing over" (p=0.02) at dose 10 mg/kg on the first interval. Passive "lying prone" increased at 3.5 and 7.0 mg/kg (p=0.0001) on the second and third time intervals. "Evasion" was decreased by 7 mg/kg on the second time interval (p=0.013).

NBQX affected significantly the RFs of behavioral elements (WL=4.62, p=0.001) and categories (WL=3.52, p=0.001). Ambivalent aggression increased ($F_{3,107}$=12.42, p=0.0001) at 3.5 mg/kg due to "tail rattling" (p=0.0001) and "threat" (p=0.001). Ambivalent stances increased (p=0.01) at 10.0 mg/kg due to increased "vertical stances" (p=0.0001). Passive "lying prone" was increased by 3.5 and 7.0 mg/kg (p=0.0001). "Climbing over" increased at 10 mg/kg (p=0.005). "Grooming of partner" decreased at dose 3.5 mg/kg (p=0.04).

3.5.. Effects of GYKI 52466

3.5.1. TA mice

Total durations of the behavioral categories were significantly affected by GYKI 52466 (WL=4.45, p=0.001), but not by time interval or interaction (p=0.13 and p=0.84, respectively). Consummate aggression was decreased by 2.5 and 5.0 mg/kg ($F_{2,80}$=7.13, p=0.002) due to decreased "biting" and "boxing" (p=0.001 and p=0.02, respectively). Non-aggressive contacts with a partner increased at the dose of 2.5 mg/kg (p=0.004) due to "grouping together with partner" (p=0.0001). The increased Ambivalent stances (p=0.01) at 5.0 mg/kg was due to the changes of "vertical stances" (p=0.048) and "lateral stances" (p=0.005). Defense was increased by 5.0 mg/kg (p=0.04). "Chasing" was increased by 2.5 mg/kg (p=0.03). "Lying with sniffing" was increased by both doses (p=0.0001).

The alterations of TFs for behavioral categories and pooled behavioral elements depended on GYKI 52466 effect only (WL=3.06, p=0.001 and WL=5.27, p=0.02, respectively). Consummate aggression was decreased by both 2.5 and 5.0 mg/kg doses ($F_{2,80}$=5.35, p=0.009) due to decreased "biting" (p=0.005) and "boxing" (p=0.04). The elements of Ambivalent aggression "rushing to attack" and "threat" were decreased by 2.5 mg/kg (p=0.001 and p=0.014, respectively). The increased Non-aggressive contacts with a partner was marked at the dose of 2.5 mg/kg (p=0.014) due to the changes of "climbing under" (p=0.0001) and "grouping with partner" (p=0.004). Also, the dose of 2.5 mg/kg induced increased "grooming of partner" (p=0.004) and "stretched attend posture" (p=0.0001). Ambivalent stances were increased by 5 mg/kg (p=0.003). "Lying with sniffing" was increased by both GYKI 52466 doses (p=0.047). Active defense "kicking of partner" increased at the dose of 5 mg/kg (p=0.03).

Also the changes in RFs depended on the drug effect only (WD=4.076, p=0.0001). Consummate aggression was decreased by both GYKI 52466 doses ($F_{2,80}$=8.39, p=0.001) due to the decreased "biting" (p=0.0001) and "boxing" (p=0.009). Non-aggressive contacts with a partner increased (p=0.006) at 2.5 mg/kg due to the increased "climbing under" (p=0.0001) and "grouping with partner" (p=0.0001). "Stretched attend posture" (p=0.0001), "grooming of partner" (p=0.0001) and "chasing" (p=0.003) were increased by 2.5 mg/kg. Defense (p=0.006) by "freezing" (p=0.01) and Ambivalent stances (p=0.005) by "lateral stances" (p=0.002) were increased by 5.0 mg/kg. Also, this dose led to increased "sitting with sniffing" (p=0.0001), but decreased "sniffing of partner's anogenital area" (p=0.01) that was the cause of change on Partner exploration (p=0.006).

3.5.2. TNA mice

The TDs of behavioral categories were affected by significant GYKI 52466 effect only (WL=4.01, p=0.0001). These effects were rather minor, since only Partner exploration was decreased by 2.5 and 5.0 mg/kg ($F_{2,80}$=12.4, p=0.0001) and Ambivalent stances increased at 5.0 mg/kg (p=0.0001). The analysis to identify element-specificity changes was failed.

A similar situation was found for TF and RF measurements, since their alterations depended on the GYKI 52466 effect only (WL=2.57, p=0.005 and WL=3.42, p=0.0001, respectively). Partner exploration was decreased by both doses ($F_{2,80}$=10.8, p=0.0001 for TF measurement and $F_{2,80}$=6.56, p=0.004 for RF measurement) and Ambivalent stances increased by 5.0 mg/kg (p=0.01 for both TF and RF measurements). In addition, TF of Locomotion was decreased (p=0.02) by 5.0 mg/kg, while RF of Defense was increased by both doses (p=0.003).

3.6. Discrimination analyses of AMPA antagonist effects on the behavioral elements in TA and TNA mice

Discrimination analysis of the effects of all AMPA antagonist (CNQX, NBQX and GYKI 52466) vs. saline built on behavioral elements was successful for all drugs and both mouse lines: 69–94% of original grouped cases and 78–92% of cross-validated grouped cases were classified correctly using various functions. In the TA mice, CNQX vs. saline effects were discriminated with a 4-component function [F=0.57×(TD_grooming of partner, GrPr)−0.5×(TD_Evasion, EV)−1.01×(RF_quick locomotion, QL)+0.95×(RF_rears, R)], where TD and RF are total duration and relative frequency of the elements. In the TNA mice, CNQX vs. saline effects could be explained by an 8-component function: F=0.52×(TD_approach, App)+1.34×(TD_locomotion with sniffing, LSn)+0.5×(TD_grooming of partner, GrPr)+0.97×(TD_stretched attend posture, SAP)−1.84×(RF_ quick

locomotion, QL) − 0.91 × (RF_sitting, St) + 1.0 × (RF_freezing, Fz) + 1.04 × (RF_palpebral closure, plp). The NBQX effects in the TA mice could be discriminated from saline effects by a 3-component function [$F = 0.89 \times$ (TD_biting, B) + 0.58 × (TD_climbing under, CIU) + 0.89 × (TD_evasion, Ev)], and in the TNA mice by a 2-component function [$F = 0.79 \times$ (TD_palpebral closure, plp) + 1.04 × (RF_sniffing of partner's body, SnPr)]. The hypothetical functions of GYKI 52466-related behavioral profile in the TA and TNA mice were 2-component functions [$F = 1.0 \times$ (TD_boxing, Bx) + 0.99 × (RF_ boxing, Bx) and $F = 1.05 \times$ (RF_chasing, Ch) − 0.62 × (RF_lying prone, lnpr), respectively].

4. Discussion

Social behavior of TA mice, selectively bred for high aggressiveness, was mostly based on aggressive elements, which occupied about 75% of the total duration. Aggressive components are weakly expressed in the behavior of TNA mice. Discriminant function analysis completely dissociated (100%) the behavioral profile of TA and TNA mice. This was accomplished by several specific behavioral categories, not only by Consummate and Ambivalent aggressions, but also of Defense, Locomotion and Non-aggressive contacts with a partner. This confirms that TA and TNA males have developed different behavioral strategies towards unknown males (Nyberg et al., 2004).

Previous studies have demonstrated significant differences in neurochemical and pharmacological actions of various AMPA receptor antagonists (e.g., Czlonkowska et al., 1997; Ozawa et al., 1998; Mead and Stephens, 1999). Behavioral effects of the competitive AMPA receptor antagonist CNQX have clearly been non-selective, dependent not only on the blockade of AMPA-type glutamate receptors but also on the blockade of kainate and *N*-methyl- d-aspartate (NMDA) receptors (Mead and Stephens, 1999; Brickley et al., 2001; Maccaferri and Dingledine, 2002). The non-competitive antagonist of NMDA receptors MK-801 increases aggressiveness in wild-type mice (McAllister, 1990), which has not been detected for CNQX having antagonistic efficacy at the glycine site of NMDA receptor (Sheardown et al., 1990; Lees, 2000; Nikam and Kornberg, 2001). MK-801 reduces also ambivalent behaviors consistent with approach-avoidance conflict (McAllister, 1990), while in the present study (see Table 2), CNQX reduced only the biting element of the Consummate aggression and did not affect ambivalent aggression. CNQX increased risk-assessment behavior in both mouse lines and dominant-defensive conflict especially in TA mice. It seems that social effects of CNQX were not relate to glycine-site antagonism of NMDA receptors.

Another competitive antagonist NBQX, which is considered a more selective AMPA antagonist than CNQX (Yu and Miller, 1995), although both of them may increase $GABA_A$ receptor-mediated postsynaptic currents (Brickley et al., 2001). It also reduced Consummate aggression in the TA mice, but increased Ambivalent aggression in the TNA mice. The negative allosteric modulator, non-competitive antagonist GYKI 52466, a more selective AMPA antagonist, ineffective at $GABA_A$ receptor-mediated postsynaptic currents (Brickley et al., 2001), affected only Consummate, but not Ambivalent aggression in the TA (or TNA) mice. Furthermore, the actions of CNQX and the other antagonists differed so that, e.g., Defense, Partner exploration, Ambivalent stances and Non-aggressive contacts with a partner were less affected by it in the TA animals than in the TNA mice, while the actions of NBQX and GYKI 52466 were robust on these behaviors in both mouse lines. These data clearly indicate that the efficacy of various AMPA antagonists differs in these mouse lines that have been bidirectionally selected for offensive aggression. However, the AMPA antagonists also shared many effects and did not show any opposite efficacies within the mouse lines.

The differences between mouse lines in drug effects on social behavior may depend, e.g., on basal activity of dopaminergic, noradrenergic, GABAergic and serotonergic systems that are different between aggressive and non-aggressive mice (Kudriavtseva and Bakshtanovskaia, 1991; Serova and Naumenko, 1996; Popova, 2006). Actually, more noradrenaline in the brain stem and less 5-HT in for forebrain have been identified in TA than TNA male mice (Lagerspetz et al., 1968). AMPA receptor functions between the TA and TNA mice have not been studied. GYKI 52466, a more selective AMPA antagonist compound than CNQX and NBQX (Yu and Miller, 1995; Lees, 2000), affected aggressive behavior the most. Boxing, a dominant consummate aggressive component, was identified as the principal element to differentiate saline- and GYKI 52466-treated TA mice. This result suggests a selective anti-aggressive property of the ligand in highly aggressive animals. "Boxing" scores were not affected by NBQX and CNQX, although all drugs reduced the "biting" component of the consummate aggression. Interestingly, GYKI 52466 may strongly affect the dopaminergic system, as, e.g., sub-chronic treatment of GYKI 52466, but not of CNQX, changes dopamine D2 receptor mRNA level in the striatum (Healy and Meador-Woodruff, 1999).

NBQX suppressed Consummate aggression and Partner exploration preceding aggression but increased vertical exploratory activity ("rearing") in TA mice. This behavioral combination can be interpreted as an attempt to avoid the situation (Blanchard et al., 1998) and it might also be discussed as increased anxiety state. Anxiogenic properties of NBQX at a smaller dose range have been earlier found in the elevated plus-maze test with C57BL/6 mice (Karcz-Kubicha and Liljequist, 1995), but not in rats in the open field test (Czlonkowska et al., 1997). CNQX increased risk assessment behavior "stretched attend posture" and defensive "freezing" in both TA and TNA lines, which suggests development of anxiety by CNQX. GYKI 52466 increased Ambivalent stances and Defense, which (together with decreased Partner exploration in the TNA mice) also suggests increased anxiety. Thus, these observations, in combination with increased Non-aggressive contacts with partner, might result from drug-induced intensified reactivity to a unfamiliar partner and from a conflicting set of motivations (Sankoorikal et al., 2006).

It is also important to link the aggression-suppressive properties of GYKI 52466 and, partly those of CNQX and NBQX, with their inhibitory influences on drug addiction-associated behaviors, such as cocaine- (Witkin, 1993; Jackson

et al., 1998) and amphetamine-induced (Witkin, 1993; Vanover, 1998) hyperlocomotion, cocaine sensitization and self-administration (Jackson et al., 1998), amphetamine (Mead et al., 1999) and ethanol (Broadbent et al., 2003) sensitization. A property of GYKI 52466 to increase acute hyperactivity and stereotypy induced by apomorphine and cocaine seem to separate it from CNQX and NBQX that are non-effective in that case (Maj et al., 1995a,b). For comparison, reduced naloxone-precipitated withdrawal symptoms as well as decreased development of tolerance to morphine have been observed in mice deficient for GluR-A subunit-containing AMPA receptors (Vekovischeva et al., 2001). It seems that drug-dependent behavior and aggressive expressions might correlate with each other (Swann, 2003) and are modulated by AMPA receptor. Thus, one of the personality features regulating expressions of "antisocial" aggression and drug-taking behavior, impulsivity (Evenden, 1999; Swann, 2003), might be modulated by AMPA receptors. In keeping, in the present study, all the AMPA antagonists decreased "biting" in the aggressive mice.

In conclusion, the results obtained here with AMPA receptor antagonists and our earlier findings on an AMPA receptor subtype-deficient mouse line (Vekovischeva et al., 2004) indicate that AMPA-type glutamate receptors modulate aggressive patterns of mouse social behavior.

Acknowledgements

The study was supported by the Academy of Finland and the Finnish Foundation of Alcohol Studies.

References

Blanchard RJ, Hebert MA, Dulloog L, Kaawaloa N, Nishimura O, Blanchard DC. Acute cocaine effects on stereotype and defense: an ethoexperimental approach. Neurosci Biobehav Rev 1998;23: 179–88.

Brickley SG, Farrant M, Swanson GT, Cull-Candy SG. CNQX increases GABA-mediated synaptic transmission in the cerebellum by an AMPA/kainate receptor-independent mechanism. Neuropharmacology 2001;41: 730–6.

Broadbent J, Kampmueller KM, Koonse SA. Expression of behavioral sensitization to ethanol by DBA/2J mice: the role of NMDA and non-NMDA glutamate receptors. Psychopharmacology (Berl) 2003;167: 225–34.

Czlonkowska A, Siemiatkowski M, Plaznik A. Some behavioral effects of AMPA/kainate receptor agonist and antagonists. J Physiol Pharmacol 1997;48: 479–88.

Davidson RJ, Jackson DC, Kalin NH. Emotion, plasticity, context, and regulation: perspectives from affective neuroscience. Psychol Bull 2000;126: 890–909.

de Waal FB. Evolutionary ethics, aggression, and violence: lessons from primate research. J Law Med Ethics 2004;32: 18–23.

Evenden JL. Varieties of impulsivity. Psychopharmacology (Berl) 1999;146: 348–61.

Gingrich JA, Hen R. Dissecting the role of the serotonin system in neuropsychiatric disorders using knockout mice. Psychopharmacology (Berl) 2001;155: 1–10.

Healy DJ, Meador-Woodruff JH. Glutamatergic modulation of subcortical motor and limbic circuits. Ann N Y Acad Sci 1999;877: 684–7.

Jackson A, Mead AN, Rocha BA, Stephens DN. AMPA receptors and motivation for drug: effect of the selective antagonist NBQX on behavioural sensitization and on self-administration in mice. Behav Pharmacol 1998;9: 457–67.

Karcz-Kubicha M, Liljequist S. Evidence for an anxiogenic action of AMPA receptor antagonists in the plus-maze test. Eur J Pharmacol 1995;279: 171–7.

Keinanen K, Wisden W, Sommer B, Werner P, Herb A, Verdoorn TA, et al. A family of AMPA-selective glutamate receptors. Science 1990;249: 556–60.

Kudriavtseva NN, Bakshtanovskaia IV. The neurochemical control of aggression and submission. Zh Vyssh Nerv Deiat Im I P Pavlova 1991;41: 459–66.

Lagerspetz KM. Studies on the aggressive behaviour of mice. Ann Acad Sci Fenn B 1964 133 pp.

Lagerspetz KM, Lagerspetz KY. Changes in the aggressiveness of mice resulting from selective breeding, learning and social isolation. Scand J Psychol 1971;12: 241–8.

Lagerspetz KM, Raitis P, Tirri R, Lagerspetz KY. Experiments concerning the transfer of a learned response and activity level by brain homogenates. Scand J Psychol 1968;9: 225–9.

Lees GJ. Pharmacology of AMPA/Kainate receptor ligands and their theraupeutic potential in Neurological and psychiatric disorders. Drugs 2000;59: 33–78.

Leighty RE, Nilsson LN, Potter H, Costa DA, Low MA, Bales KR, et al. Use of multimetric statistical analysis to characterize and discriminate between the performance of four Alzheimer's transgenic mouse lines differing in Abeta deposition. Behav Brain Res 2004;153: 107–21.

Lopez NL, Vazquez DM, Olson SL. An integrative approach to the neurophysiological substrates of social withdrawal and aggression. Dev Psychopathol 2004;16: 69–93.

Maccaferri G, Dingledine R. Complex effects of CNQX on CA1 interneurons of the developing rat hippocampus. Neuropharmacology 2002;43: 523–9.

Maj J, Rogoz Z, Skuza G, Jaros T. Some behavioral effects of CNQX AND NBQX, AMPA receptor antagonists. Pol J Pharmacol 1995a;47: 269–77.

Maj J, Rogoz Z, Skuza G, Kolodziejczyk K. Some central effects of GYKI 52466, a non-competitive AMPA receptor antagonist. Pol J Pharmacol 1995b;47: 501–7.

McAllister KH. Ethological analysis of the effects of MK-801 upon aggressive male mice: similarity to chlordiazepoxide. Pharmacol Biochem Behav 1990;37: 101–6.

Mead AN, Stephens DN. CNQX but not NBQX prevents expression of amphetamine-induced place preference conditioning: a role for the glycine site of the NMDA receptor, but not AMPA receptors. J Pharmacol Exp Ther 1999;290: 9–15.

Mead AN, Vasilaki A, Spyraki C, Duka T, Stephens DN. AMPA-receptor involvement in c-fos expression in the medial prefrontal cortex and amygdala dissociates neural substrates of conditioned activity and conditioned reward. Eur J Neurosci 1999;11: 4089–98.

Miczek KA, Maxson SC, Fish EW, Faccidomo S. Aggressive behavioral phenotypes in mice. Behav Brain Res 2001;125: 167–81.

Miczek KA, Fish EW, De Bold JF, De Almeida RM. Social and neural determinants of aggressive behavior: pharmacotherapeutic targets at serotonin, dopamine and gamma-aminobutyric acid systems. Psychopharmacology (Berl) 2002;163: 434–58.

Nikam SS, Kornberg BE. AMPA receptor antagonists. Curr Med Chem 2001;8: 155–70.

Nyberg JM, Vekovischeva O, Sandnabba NK. Anxiety profiles of mice selectively bred for intermale aggression. Behav Genet 2003;33: 503–11.

Nyberg J, Sandnabba K, Schalkwyk L, Sluyter F. Genetic and environmental (inter)actions in male mouse lines selected for aggressive and nonaggressive behavior. Genes Brain Behav 2004;3: 101–9.

Ozawa S, Kamiya H, Tsuzuki K. Glutamate receptors in the mammalian central nervous system. Prog Neurobiol 1998;54: 581–618.

Popova NK. From genes to aggressive behavior: the role of serotonergic system. Bioessays 2006;28: 495–503.

Poshivalov VP, Suchotina IA, Verbitzkaya EV. Ethological pharmacology of anxiogenic and anxiolytic drugs. Ann Ist Super Sanita 1988;24: 453–9.

Sandnabba NK. Selective breeding for isolation-induced intermale aggression in mice: associated responses and environmental influences. Behav Genet 1996;26: 477–88.

Sankoorikal GM, Kaercher KA, Boon CJ, Lee JK, Brodkin ES. A mouse model system for genetic analysis of sociability: C57BL/6J versus BALB/cJ inbred mouse strains. Biol Psychiatry 2006;59: 415–23.

Serova LI, Naumenko EV. Involvement of the brain catecholaminergic system in the regulation of dominant behavior. Pharmacol Biochem Behav 1996;53: 285–90.

Sheardown MJ, Nielsen EO, Hansen AJ, Jacobsen P, Honore T. 2,3-Dihydroxy-6-nitro-7-sulfamoyl-benzo(*F*)quinoxaline: a neuroprotectant for cerebral ischemia. Science 1990;247: 571–4.

Siegel A, Roeling TA, Gregg TR, Kruk MR. Neuropharmacology of brain-stimulation-evoked aggression. Neurosci Biobehav Rev 1999;23: 359–89.

Sluyter F, Arseneault L, Moffitt TE, Veenema AH, de Boer S, Koolhaas JM. Toward an animal model for antisocial behavior: parallels between mice and humans. Behav Genet 2003;33: 563–74.

Stephens DN, Brown G. Disruption of operant oral self-administration of ethanol, sucrose, and saccharin by the AMPA/kainate antagonist, NBQX, but not the AMPA antagonist, GYKI 52466. Alcohol Clin Exp Res 1999;23: 1914–20.

Swann AC. Neuroreceptor mechanisms of aggression and its treatment. J Clin Psychiatry 2003;64(Suppl 4): 26–35.

Vanover KE. Effects of AMPA receptor antagonists on dopamine-mediated behaviors in mice. Psychopharmacology (Berl) 1998;136: 123–31.

Vekovischeva OY, Zamanillo D, Echenko O, Seppala T, Uusi-Oukari M, Honkanen A, et al. Morphine-induced dependence and sensitization are altered in mice deficient in AMPA-type glutamate receptor-A subunits. J Neurosci 2001;21: 4451–9.

Vekovischeva OY, Aitta-Aho T, Echenko O, Kankaanpaa A, Seppala T, Honkanen A, et al. Reduced aggression in AMPA-type glutamate receptor GluR-A subunit-deficient mice. Genes Brain Behav 2004;3: 253–65.

Witkin JM. Blockade of the locomotor stimulant effects of cocaine and methamphetamine by glutamate antagonists. Life Sci 1993;53: PL405–10.

Yu W, Miller RF. NBQX, an improved non-NMDA antagonist studied in retinal ganglion cells. Brain Res 1995;692: 190–4.

Zamanillo D, Sprengel R, Hvalby O, Jensen V, Burnashev N, Rozov A, et al. Importance of AMPA receptors for hippocampal synaptic plasticity but not for spatial learning. Science 1999;284: 1805–11.