Pharmacological Reports 67 (2015) 928–933

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Original research article

Partial effects of the AMPAkine CX717 in a strain specific battery of tests for manic-like behavior in black Swiss mice

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ARTICLE INFO

Article history:
Received 28 December 2014
Received in revised form 30 January 2015
Accepted 19 February 2015
Available online 4 March 2015

Keywords:
Affective disorders
Mania
Animal model
Behavior
AMPA receptors

ABSTRACT

Background: AMPA receptors are highly expressed throughout the central nervous system and are suggested to be involved in mood regulation. Studies found changes in glutamate, its metabolites and receptors in patients with bipolar disorder (BPD) or major depression (MD) and in animal models of stress. Additional data suggest that the glutamatergic system and AMPA receptors specifically, have an important role in modulating the therapeutic effects of mood stabilizers. Further research on the role of AMPA receptors in mood regulation can be done using AMPAkines, positive modulators of AMPA receptors. AMPAkines have been studied for cognitive enhancement in neurodegenerative disorders and some were also examined in preclinical studies of mood disorders. In that context, the present study was designed to test the effects of the AMPAkine CX717 in a strain specific battery of tests for mania-like behaviors.

Methods: Black Swiss male mice were sub-chronically treated with 5 different doses of CX717 or vehicle and tested in a battery of behavioral tests including spontaneous activity, sweet solution preference, resident-intruder, forced swim and amphetamine-induced hyperactivity.

Results: Data show that CX717 doses of 30 mg/kg and above, but not lower, reduce activity levels. Moreover, 45 mg/kg and above reduce interactions in the resident-intruder test and ameliorate amphetamine-induced hyperactivity.

Conclusions: The results therefore show a partial effect of CX717 on manic-like behavior, somewhat similar to previously demonstrated effects of atypical antipsychotic drugs in this strain. It is therefore suggested that further work related to AMPAkines in the treatment of affective disorders might be warranted.

Introduction

Affective disorders, major depression (MD) and bipolar disorder (BPD) are serious mental illnesses with high prevalence and significant impact on patients, their families and the entire society. Despite the importance of affective disorders, little is known about their underlying mechanisms or the way by which effective medications exert their effect. One interesting hypothesis regarding the pathophysiology of mood disorders is that at least in part they are caused by impaired neuronal plasticity in the brain [1] and one system that might be relevant to these changes is the glutamate system [2]. Glutamate is the main excitatory neurotransmitter in the central nervous system (CNS) and plays a critical role in various forms of neuronal plasticity [1,3]. The glutamate system includes a variety of receptors amongst which is the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazoleprorionate) group of ionotropic receptors. This class of receptors mediates the majority of excitatory synaptic transmission in the CNS [3] and its trafficking plays an important function in neuronal plasticity [4,5]. AMPA receptors are highly expressed throughout the CNS, and are found mainly in regions of the brain that have been suggested to be involved in mood regulation such as the prefrontal cortex and hippocampus [5–7]. This distribution suggests that AMPA receptors may have a role in mood modulation [8].

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URL: https://www.mta.ac.il/en/lecturers/1468/Pages/default.aspx

http://dx.doi.org/10.1016/j.pharep.2015.02.008
1734-1140/

Indeed, data support the involvement of AMPA receptors in mood regulation. For example, some studies have found increased levels of glutamate in blood and frontal cortex of patients suffering from BPD or MD [9,10]; studies using brain imaging found reduced levels of glutamate in the anterior cingulate cortex of depressed patients during a depressive episode [11] as well as abnormalities in regional glutamate, glutamine and GABA in patients with depression [12]. Several studies indicated a reduction in GluR1, a subunit of the AMPA receptor, in the prefrontal cortex and striatum of subjects with BPD and MD [6,13].

Animal model studies showed increased glutamate levels in the hippocampus and amygdala in stressed animals [14,15]. Others demonstrated that prenatal stress, an animal model known to induce depression-like behavior, significantly attenuated GluR1 phosphorylation [16] and reduced mRNA expression of the glutamate transporters EAAT2 and EAAT3 in the hippocampus, striatum and frontal cortex [16]. These data are in accordance with post-mortem studies of BPD patients demonstrating reduced EAAT3 and EAAT4 transcripts expression [17].

A different set of data also suggests that the glutamatergic system and AMPA receptors specifically, have an important role in modulating the therapeutic effect of mood stabilizers. Lithium, the prototypic mood stabilizer, has diverse effects on AMPA receptors, including modulation of receptor levels in rats [3,18] and enhancement of surface cross-linked GluR1 and GluR2 in the hippocampus [19]. Both lithium and the anticonvulsant mood stabilizer valproate exert major effects on intracellular signaling cascades that regulate AMPA receptor trafficking [20,21], and lamotrigine, another anticonvulsant mood stabilizer, is thought to decrease glutamate release and increase AMPA receptor expression [12]. Moreover, a study by Gould and colleagues [19] showed that NBQX, a competitive AMPA receptor antagonist, attenuated lithium's effect in the forced swim test. An interesting recent study further supports the involvement of AMPA receptors in mood by showing that altered RNA editing efficiency of AMPA receptors results is affective-like behavioral changes in mice [22].

An additional approach to further explore AMPA receptors involvement in mood regulation is by using AMPAkines. AMPAkines are positive modulators of AMPA receptors, which bind allosterically to GluR1–GluR4 subunits and slow the rate of AMPA receptor deactivation or desensitization [23], enhance the currents and prolong the duration of AMPA receptor-mediated responses both *in vitro* and *in vivo* [12,24]. Because AMPAkines have no agonist actions the drugs are only effective with a background of transmission in progress [25]. Therefore, it is likely that their principal site of action will reflect the brain areas that are involved in ongoing behavior [26]. AMPAkines have been studied for cognitive enhancement in neurodegenerative disorders and some were also examined in preclinical studies of mood disorders [12].

Related work with animals showed that AMPAkines reduced spontaneous, unmotivated exploratory behavior in a novel or familiar environments [27], attenuated stereotypic rearing induced by methamphetamine and decreased hyperactivity induced by amphetamine [28,29] as well as methamphetamine-induced rotational behavior after sensitization [26]. Other studies have shown that AMPAkines reduced immobility in the forced swim test and the tail suspension test in mice [30,31], increased social sniffing in the mouse social approach task [32] and reduced submissive behavior [12]. Moreover, some data showed that AMPAkines increased brain-derived neurotrophic factor (BDNF) expression and cell proliferation in the CNS, suggesting a neurotrophic and neuroprotective effect [33]. These outcomes were similar to the repeatedly demonstrated effects of both mood stabilizers and antidepressant drugs on the adult brain.

Further work with animal models can contribute to the understanding of AMPAkines activity in the context of BPD but there are only few valid models for mania and for response to mood stabilizers. One model that was suggested in the last few years includes the utilization of a battery of tests representing specific behavioral domains of mania in the black Swiss mice strain. This model has relatively good face validity as black Swiss mice show a variety of mania-like behaviors compared with other strains, including high preference for sweet solution modeling increased reward seeking behavior, low anxiety levels in the light/dark box and the elevated plus-maze modeling high risk taking behavior, high aggression levels in the resident-intruder test or the social interaction test modeling aggressive and intrusive behavior, low immobility levels in the forced swim test modeling increased vigor and goal directed activity and high motor sensitivity to amphetamine modeling the enhanced sensitivity to psychostimulant drugs [34–38]. Moreover, the model has some predictive (pharmacological) validity as it responds to the mood stabilizers lithium and valproate [38] as well as to the atypical antipsychotics olanzapine, risperidone and asenapine [37,39,40] but not to the prototypic antidepressant imipramine [38]. Moreover, the model responded at least in part to interventions with compounds that are related to some of the novel ideas regarding the therapeutic actions of mood stabilizing drugs including compounds that affect GSK [39] and PKC [41] activity. Last but not least, the model has some construct (etiological) validity as it was demonstrated that compared with other mice strains, black Swiss mice have lower levels of frontal cortex beta-catenin [37], a transcription factor that had been implicated in the therapeutic effect of mood stabilizers [42].

The present study was therefore designed to use the black Swiss mice model and evaluate the possible effects of AMPAkines on affective-like behaviors in a battery of tests.

Materials and methods

Animals

Male, black Swiss (BS) mice (Taconic Farms, NY, USA), 7–8 weeks old were transported to our laboratory where experimentation started no less than 1 week later, to allow for appropriate acclimatization time. Mice were singly housed in a colony room with constant temperature (22 ± 1 °C), 12/12 light dark cycle (lights on/off at 0730/1930) and ad-lib food and water. Single housing was necessary because of the sweet solution preference test (see description below). Separate cohorts of mice were used for experiment 1 and for experiment 2. All experimental procedures were conducted according to NIH guidelines and approved by the University of Minnesota Institutional Animal Care and Use Committee (Protocol no. 0801A2581). The BS mice strain was selected for the experiments as it was repeatedly demonstrated to be an advantageous strain for the modeling of some of the domains of mania and for effects of mood stabilizing drugs [37,38].

Drugs

The AMPAkine CX717 (generously donated by Cortex Pharmaceuticals, SF, CA, USA) was dissolved in 33% HPCD solution by sonication for 1 h at 50 °C. Drug was administered to mice *via* intraperitoneal (IP) injection twice a day, at 8:00 a.m. and at 6:00 p.m., for 3 days prior to the start of behavioral experiments and throughout the days of experimentation (as described below). Doses of CX717 were 3 mg/kg, 10 mg/kg or 30 mg/kg for experiment 1 and 45 mg/kg and 60 mg/kg for experiment 2. The initial doses were selected based on previously demonstrated behavioral effects of CX717 [43] and based on unpublished information from Cortex Pharmaceuticals. The higher doses (tested in experiment 2) were selected based on the results of experiment

1. All doses were diluted to injection volume of 10 ml/kg. Control group for each experiment was treated with the same volume of 33% HPCD solution. AMPAkines were repeatedly demonstrated to cross the blood brain barrier after peripheral administration [28] and enter the brain within minutes [44]. To the best of our knowledge, the effects of CX717 on affective-like behavior in animals were not previously reported but the compound was shown to restore primate impaired cognitive performance caused by sleep deprivation [45].

Whereas AMPAkines were shown to have acute effects on rodents' behavior [26], behavioral changes that might be more relevant to affective disorders were demonstrated after a week or more of daily administration [46] and repeated administration of an AMPAkine was essential to rescue mice from neurodegenerative processes [47]. Accordingly, we selected to test a sub-acute administration regimen with 3 days of administration prior to the first behavioral test. There were a number of reasons for this selection: (1) there is only minimal previous behavioral data on the effects of CX717 on mice behavior and it is unclear whether acute administration can be effective in our model. (2) The model includes a number of tests and therefore animals receive treatment during the testing days. Hence, in this design a real acute testing is possible only for the first behavioral test and not for the following ones. (3) Previous studies with this model utilized similar designs with sub-acute drug administration prior to the first behavioral test. d-Amphetamine sulfate (SIGMA, St. Lewis, MI, USA) was dissolved in saline and injected IP at a 1.0 mg/kg dose and 10 ml/kg volume. Amphetamine was administered acutely, immediately before the start of the test. Control animals received an equal volume of saline.

Behavioral tests

Order of treatment and tests

To evaluate the behavioral effects of CX717, mice were tested in a consecutive battery of tests for mania-like behaviors, as done previously with mood stabilizers and atypical antipsychotics [37,38,40]. Tests started after 3 days of drug administration, were conducted one per day and were ordered from least to more intrusive to minimize the effects of each test on the following ones [48,49]. The order of tests was spontaneous activity, sweet solution preference, resident-intruder test, forced swim test, and amphetamine-induced hyperactivity. Specific description of these tests is detailed below. Drug administration continued throughout the days of behavioral experiments.

Spontaneous activity

Mice were placed in $50 \times 25 \times 20$ cm automated activity monitors (Opto3, Columbus Instruments, Columbus, OH, USA) for a 60 min session where activity was recorded as beam breaks using infrared detectors. At the end of the session mice were returned to their home cages and the boxes were wiped clean with a 10% alcohol solution.

Sweet solution preference test

Mice were supplied with a bottle of 1% saccharin solution (SIGMA, St. Lewis, MI, USA) for 48 h on top of the regular supply of water and food. Saccharin concentration was selected based on previous work with BS mice [35,38]. Weights of saccharin solution and water bottles were taken at the beginning of the experiment and every 24 h thereafter providing 3 measures at time zero, after 24 h and after 48 h. Sweet solution preference was calculated daily as the ratio of saccharin out of total liquid consumption.

Resident-intruder test

Resident mice were transferred in their home cages to an experimental room where cage covers were removed. After a 5-min adaptation period, a smaller, previously group-housed mouse (*i.e.*, intruder), was placed into the resident's cage and behavior was digitally recorded from above for a 10-min session. Recordings served to manually score resident's aggressive interactions (defined as attempts to bite, actual bite, boxing postures and wrestling postures) and non-aggressive social interactions (defined as other types of body contact including sniffing, allogrooming and body contact). Behaviors performed when not interacting were not scored. The resident's aggression score was calculated as the ratio of aggressive interactions out of total (aggressive + non-aggressive) interactions. At the end of the session the intruder was removed and placed back in its home cage, the resident's cage was covered and both mice were returned to the colony room. To minimize harm to animals, mice were briefly separated with a plastic probe by the experimenter when attacks became vicious and included significant biting. Hence, total attack time was not scored and only numbers of aggressive and non-aggressive interactions were scored from recordings. This method was previously shown to be sensitive enough to demonstrate the effects of mood stabilizers in this test [50].

Forced swim test (FST)

Mice were placed for a 6-min session in a vertical cylindrical plastic container (25 cm tall $\times$ 18 cm diameter), filled to a depth of 15 ± 1 cm with tap water at 22 ± 1 °C. This depth was sufficient to ensure that mice could not escape or touch the floor of the container. At the end of the session, mice were removed from the water, dried with a paper towel, and placed back in their home cage. Water in the container was changed after each session. Sessions were digitally recorded from the side and the last 4 min of each session were scored using an automated acquisition and analysis software (Biobserve, Bonn, Germany). Scored behaviors were defined as active (swim and struggle) *versus* passive (floating with only minimal movements needed to keep head above water) behaviors.

Amphetamine-induced hyperactivity

Mice were administered with amphetamine or vehicle and immediately placed in activity monitors for a 60 min session, where activity was recorded as described above for the spontaneous activity test.

Statistical analysis

Data for spontaneous activity (activity counts), sweet solution preference (preference ratio), forced swim test (immobility time) and resident intruder test (total interaction time and aggression ratio) were analyzed using one way analysis of variance (ANOVA) with CX717 dose as main factor. Data for the amphetamine-induced hyperactivity test were analyzed using two-way ANOVA with CX717 dose and amphetamine treatment as main factors. When ANOVA showed significant effects it was followed by *post hoc* LSD tests. Level of significance for all tests was set as $p \leq 0.05$.

Results

Experiment 1

As shown in Table 1, sub-chronic administration of 30 mg/kg CX717 but not the lower doses resulted in a significant reduction in spontaneous activity. None of the doses had significant effects in the sweet solution preference test, forced swim test and resident-intruder test (Table 1). As expected, amphetamine administration resulted in a significant increase in activity levels but this effect was not influenced by the administration of 3, 10 or 30 mg/kg CX717 (Table 1).

Table 1
Behavioral effects of lower doses of CX717.

Test	Vehicle	3 mg/kg	10 mg/kg	30 mg/kg	Statistics
Spontaneous activity (infrared beam breaks in 60 min)	2738 ± 107 (11)	2706 ± 277 (11)	3025 ± 241 (11)	1899 ± 222 (11)	$F(3,40) = 4.78$, $p < 0.01$; *Post hoc* 30 mg/kg ≠ all other groups
Sweet solution preference (mean preference across 48 h)	0.74 ± 0.015 (12)	0.72 ± 0.018 (12)	0.69 ± 0.02 (12)	0.72 ± 0.03 (12)	$F(3,44) = 0.48$, $p = 0.7$
Forced swim test (immobility time, s)	27 ± 8 (12)	20 ± 5 (12)	12 ± 3 (11)	24 ± 7 (12)	$F(3,43) = 1.03$, $p = 0.39$
Resident-intruder					
Total interactions	37 ± 2 (12)	32 ± 3 (12)	33 ± 3 (11)	32 ± 3 (12)	$F(3,43) = 0.72$, $p = 0.55$
Aggression ratio	0.38 ± 0.07 (12)	0.27 ± 0.05 (12)	0.29 ± 0.07 (11)	0.39 ± 0.07 (12)	$F(3,43) = 0.86$, $p = 0.47$

Test	Sal	Amph	Sal	Amph	Sal	Amph	Sal	Amph	Statistics
Amphetamine-induced hyperactivity (infrared beam breaks in 60 min); $n = 6$/group	1449 ± 240	3329 ± 527	1511 ± 223	4840 ± 914	1809 ± 457	4946 ± 1005	1979 ± 636	3173 ± 954	Amph: $F(1,40) = 23.2$, $p < 0.001$; CX717: $F(3,40) = 0.95$, $p = 0.43$; Interaction: $F(3,40) = 1.11$, $p = 0.36$

Numbers in parenthesis represent the number of animals in the group.

Table 2
Behavioral effects of higher doses of CX717.

Test	Vehicle	45 mg/kg	60 mg/kg	Statistics
Spontaneous activity (infrared beam breaks in 60 min)	3261 ± 264 (10)	1518 ± 192 (10)	2301 ± 286 (10)	$F(2,27) = 12.13$, $p < 0.001$ *Post hoc* 45 mg/kg ≠ veh ($p < 0.001$); 60 mg/kg ≠ veh ($p < 0.02$); 45 mg/kg ≠ 60 mg/kg ($p < 0.04$)
Sweet solution preference (mean preference across 48 h)	0.68 ± 0.01 (10)	0.65 ± 0.03 (10)	0.65 ± 0.02 (10)	$F(2,27) = 0.6$, $p = 0.56$
Forced swim test (immobility time, s)	60 ± 19 (10)	45 ± 11 (10)	52 ± 11 (10)	$F(2,27) = 0.16$, $p = 0.85$
Resident-intruder				
Total interactions	39 ± 2 (10)	25 ± 3 (10)	21 ± 5 (10)	$F(2,27) = 7.4$, $p < 0.003$. *Post hoc*: Veh ≠ 45 mg/kg ($p < 0.01$); Veh ≠ 60 mg/kg ($p < 0.001$)
Aggression ratio	0.25 ± 0.06 (10)	0.37 ± 0.06 (10)	0.27 ± 0.07 (10)	$F(2,27) = 1.1$, $p = 0.36$

Test	Sal	Amph	Sal	Amph	Sal	Amph	Statistics
Amphetamine-induced hyperactivity (infrared beam breaks in 60 min); $n = 6$/group	1733 ± 439 ($n = 5$)	8127 ± 1108 ($n = 4$)	2116 ± 453 ($n = 4$)	2067 ± 513 ($n = 5$)	2318 ± 270 ($n = 5$)	2190 ± 376 ($n = 4$)	Amph: $F(1,23) = 16.8$, $p < 0.001$; CX717: $F(2,23) = 13.6$, $p < 0.001$; Interaction: $F(2,23) = 18.7$, $p < 0.001$. *Post hoc*: Veh-Amph ≠ all other groups ($p < 0.001$)

Numbers in parenthesis represent the number of animals in the group.

Experiment 2

As demonstrated in Table 2, the sub-chronic administration of higher doses of CX717, both 45 and 60 mg/kg, resulted in a significant reduction in spontaneous activity, significant reduction in total interactions in the resident-intruder test and significant amelioration of amphetamine-induced hyperactivity. CX717 had no effects in the sweet solution preference test, in the forced swim test and on the aggression measure in the resident-intruder test (Table 2).

Discussion

The present data demonstrate that sub-chronic administration of higher doses of CX717 result in the amelioration of some manic-like behaviors in black Swiss mice. These behaviors include spontaneous activity, number of interactions in the resident-intruder test and amphetamine-induced hyperactivity. CX717 did not affect sweets solution preference or immobility time in the forced swim test and did not influence the aggression ratio in the resident-intruder test.

Previous work in the BS mice strain showed that similar batteries of tests can distinguish the effects of different drugs used for BPD. Whereas lithium had an effect to reduce sweet solution preference and attenuate amphetamine-induced hyperactivity, it had no effect on spontaneous activity, in the FST, in the light/dark box or in the resident-intruder test [38]. Treatment with valproate had a different profile and it reduced sweet solution preference and increased immobility time in the FST but had no effect on spontaneous activity, amphetamine-induced hyperactivity, light/dark box or resident-intruder tests [38]. An additional drug that is used in the treatment of mania, the atypical antipsychotic risperidone, was effective only in the amphetamine-induced hyperactivity test [37] whereas another atypical antipsychotic, asenapine reduced amphetamine-induced hyperactivity and decreased vigor in the FST [40]. Hence, the fact that CX717 did not affect the entire battery does not preclude its possible antimanic potential.

BPD includes both mania and depression and the current study examined the effects of CX717 in a battery of behavioral tests representing manic-like behavior but not in other tests that represent depression-like behavior. However, a number of

different AMPAkines were previously demonstrated to have antidepressant-like effects in animals including reduction in immobility in the FST and TST [30,31], increase in social behavior [32] and reduction in submissive behavior [46]. Moreover, AMPAkines induced increase in BDNF expression and cell proliferation in the adult brain [33]. These effects are similar to those demonstrated for antidepressant drugs when used in similar tests [51,52]. In addition, AMPAkines were shown to have some antimanic-like effects in animal models including attenuation of stereotypic rearing after an acute methamphetamine injection [28], decrease in amphetamine-induced hyperactivity [29] and reduction in methamphetamine sensitization-induced rotational behavior [26]. Taken together, these data suggest that AMPAkines may have both antidepressant-like and antimanic-like effects and therefore might fulfill the definition of a mood stabilizer. Our current data support this possibility.

The present study describes behavioral changes under drug treatment and therefore cannot implicate any specific mechanism by which CX717 exerts its effects. Leading theories suggest that the effects of manipulating the glutamatergic system in mood disorders are related to enhancing synaptic plasticity and cellular resilience [53]. Indeed AMPAkines were demonstrated to increase synaptic plasticity and increase BDNF levels [33,47]. As increased plasticity had been repeatedly implicated as a central mechanism in the therapeutic effects of mood stabilizers [54] it is possible to hypothesize that this is the mechanism through which CX717 acts to alter behavior in the present study. Further experiments are needed to examine this possibility.

It is possible that some limitations may hinder the ability to interpret the present results. One limitation is the fact that CX717 reduced spontaneous locomotion in the open field test. This reduction might suggest a generalized effect on activity levels and consequently influence the results in other tests, including the social interaction and the amphetamine-induced hyperactivity tests. However, in the BS strain, baseline locomotor activity is higher than in some other strains [38,55] and therefore can be considered a part of their manic-like profile that is modified by potential mood stabilizers [41]. Moreover, higher baseline activity that is modified after mood stabilizers treatment is also shown in other mice strain-based models for mania [56]. Moreover, reduction in activity levels of rodent models is not an uncommon feature for antimanic drugs and is in fact quite typical to treatment with atypical antipsychotic drugs that are considered today first line medication for bipolar mania [57]. For example, both clozapine and olanzapine were demonstrated to reduce spontaneous activity as well as drug-induced activity [58]. Yet, at least for the higher doses, the effects of CX717 to reduce amphetamine-induced hyperactivity were much larger after amphetamine than for spontaneous activity. In the spontaneous activity test the 45 mg/kg dose reduced activity by approximately 50% and the 60 mg/kg dose reduced activity by approximately 30% but for the amphetamine-hyperactivity test both the 45 mg/kg and the 60 mg/kg doses reduced activity by 75% (Table 2). One more point that suggests that the effects on spontaneous activity are not a significant limitation is that these effects were demonstrated only in the first test but not in the control (non-amphetamine animals) tested in the amphetamine-hyperactivity test (Table 2). Accordingly, it may be suggested that the effects in the first test are more related to exploration rather than activity or that the effects on general activity tolerate across the additional treatment days. Regardless of the possible reasons, CX717 did not reduce locomotor activity levels of the non-amphetamine mice during the amphetamine-induced hyperactivity test suggesting that the effects are specific to the mania-like behavior.

Another limitation of the present study is the absence of CX717 brain level measurements or a measure of AMPA receptor activity. CX717 was administered *via IP* injections (*i.e.* administered peripherally) and because brain levels or activity were not evaluated we cannot assure it reached the target brain areas or acted there. Yet, AMPAkines were repeatedly demonstrated to cross the BBB and reach the brain within minutes after peripheral administration [44,59]. Additionally, the administration of CX717 was previously demonstrated to have behavioral effects suggesting it crossed into the brain [43,60].

Additional constraint of the present study is that CX717 was administered only in a sub-chronic regimen whereas affective disorders are chronic illnesses that require chronic treatment and most mood stabilizers and antidepressants exert their therapeutic effect only after weeks of treatment [61]. Therefore, to better simulate the disorders and their treatment, it might have been beneficial to also test the effects of chronic administration. Nevertheless, other drugs that act on the glutamatergic system were found to have a rapid antidepressant effect after acute administration [12] and it is possible that glutamatergic compounds may act on mood faster than serotonergic or noradrenergic drugs, suggesting a therapeutic advantage to those drugs. However, this suggestion needs careful examination because acute administration of serotonergic and noradrenergic agents was also shown to have antidepressant-like effect in animal models [62].

Conclusion

In accordance with previous results with other AMPAkines, the data presented here support an antimanic-like effect of CX717. It is therefore postulated that AMPAkines may present a group of compounds with potential application as mood stabilizers. Further exploration of the range of effects of these compounds on behavior and on brain systems related to affective disorders is still needed to examine this possibility but considering the need for novel and more efficacious mood stabilizers, such exploration might be of significant value.

Funding

There was no external funding available to support this study.

Conflict of interest

Authors declare no conflict of interest relevant to this study. Prof. Einat and Dr. Flaisher-Grinberg are faculty members in academic institutions with no other sources of income or relationship with external companies. Ms. Kara is a Ph.D. student in Prof. Einat's laboratory and is not receiving any income from non-academic resources. None of the authors has any financial and personal relationships with other people or organizations that could inappropriately influence (bias) the work.

Acknowledgement

The authors would like to thank Cortex Pharmaceuticals for the free supply of CX717.

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