GLYX-13 (rapastinel) ameliorates subchronic phencyclidine- and ketamine-induced declarative memory deficits in mice

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Abstract

GLYX-13 (rapastinel), a tetrapeptide (Thr-Pro-Pro-Thr-amide), has been reported to have fast acting antidepressant properties in man based upon its \textit{N}-methyl-\textit{D}-aspartate receptor (NMDAR) glycine site functional partial agonism. Ketamine, a non-competitive NMDAR antagonist, also reported to have fast acting antidepressant properties, produces cognitive impairment in rodents and man, whereas rapastinel has been reported to have cognitive enhancing properties in rodents, without impairing cognition in man, albeit clinical testing has been limited. The goal of this study was to compare the cognitive impairing effects of rapastinel and ketamine in novel object recognition (NOR), a measure of declarative memory, in male C57BL/6J mice treated with phencyclidine (PCP), another NMDAR noncompetitive antagonist known to severely impair cognition, in both rodents and man. C57BL/6J mice given a single dose or subchronic ketamine (30 mg/kg, i.p.) showed acute or persistent deficits in NOR, respectively. Acute i.v. rapastinel (1.0 mg/kg), did not induce NOR deficit. Pre-treatment with rapastinel significantly prevented acute ketamine-induced NOR deficit. Rapastinel (1.0 mg/kg, but not 0.3 mg/kg, iv) significantly reversed both subchronic ketamine- and subchronic PCP-induced NOR deficits. Rapastinel also potentiated the atypical antipsychotic drug with antidepressant properties, lurasidone, to restore NOR in subchronic ketamine-treated mice. These findings indicate that rapastinel, unlike ketamine, does not induce a declarative memory deficit in mice, and can prevent or reverse the ketamine-induced NOR deficit. Further study is required to determine if these differences translate during clinical use of ketamine and rapastinel as fast acting antidepressant drugs and if rapastinel could have non-ionotropic effects as an add-on therapy with antipsychotic/antidepressant medications.

Keywords

Rapastinel; GLYX-13; Ketamine; Novel object recognition; Depression; PCP

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1. Introduction

Rapastinel, an NMDA receptor modulator with glycine-site partial agonist properties [1], has been reported to have rapidly acting antidepressant properties [2]. Ketamine, an NMDAR non-competitive antagonist, has also been reported to produce rapidly acting antidepressant properties [3]; however, it also causes dissociative and psychotic-like effects, as well as cognitive impairment, in healthy humans [4,5], and exacerbates psychosis, but not cognitive impairment, in patients with schizophrenia [6-8]. Ketamine also causes deficits in cognition in rodents, including novel object recognition (NOR), an analog of human declarative memory [9]. NOR is dependent on the integrated action of the hippocampus, entorhinal, perirhinal and temporal association cortices, and prefrontal cortex [10].

By contrast with ketamine, rapastinel has been reported to enhance hippocampal-dependent spatial learning tasks in rodents [11], indicating it may have cognitive enhancing, as well as antidepressant properties [1]. However, there is no data on the effects of rapastinel on neuropsychological test performance in normal volunteers or patients with depression.

Glutamate, via its actions at NMDAR and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) receptors, has a profound effect on synaptic plasticity and, thus, plays a major role in learning and memory [12]. Subchronic treatment with the NMDAR antagonist, phencyclidine (PCP), induces significant deficits in NOR in both rats and mice [13-16]. This deficit is reversed by atypical antipsychotic drugs (AAPDs), including lurasidone [16], which is also an effective antidepressant in patients with bipolar depression [17] and has a small, but statistically significant effect, on depression ratings in patient with schizophrenia as well [18].

The goal of this study was to assess the effects of rapastinel on NOR in C57BL/6J mice and to determine if it could block or reverse the cognitive impairing effect of ketamine and PCP on NOR.

We chose ketamine rather than PCP for some experiments since ketamine and rapastinel are both being developed as antidepressants but PCP is not. We chose PCP for some studies to show that ketamine is like PCP and both impair cognition whereas rapastinel does not. We also sought to determine the interaction of rapastinel with the AAPD/antidepressant, lurasidone, due to its potential as an add-on therapy.

2. Materials and methods

2.1. Animals

Three cohorts of male C57BL/6J mice (2–1/2–3 month old, Jackson, MA, USA), N = 40, 45, and 48 were used in experiments 1–3 respectively. Mice were group housed (five/cage) in a controlled environment held at 21 ± 2 °C and 50 15% relative humidity with a 14:10 h light–dark period (lights on: ±05:00 am). All experiments were conducted during the light phase. Food and water were available ad libitum. The mice were habituated to the colony upon arrival for a week, during which time, they were not handled. All experiments were
conducted in accordance with Institutional Animal Care and Use Committee of Northwestern University, Chicago.

2.2. Drugs

Rapastinel was obtained from SAI Life Sciences (India). PCP was a generous gift from National Institute of Drug Abuse. Ketamine was purchased from Sigma–Aldrich (St. Louis, MO). Lurasidone was provided by Sumitomo Dainippon Pharma Co., Ltd. (Osaka, Japan). Rapastinel, PCP, and ketamine were dissolved in 0.9% sterile saline (Sal). PCP and ketamine were administered intraperitoneally (ip), at a volume of 10 mL/kg body weight. Rapastinel was given intravenously (iv). The dose of rapastinel (1.0 mg/kg) was chosen because it produced optimal enhancement in learning in both young adult and aged rats [11] and in a trace eye blink conditioning task in rabbits [19]. The doses for ketamine (30 mg/kg) and PCP (10 mg/kg) were chosen based on prior studies, which showed that these doses induce significant cognitive impairment in mice and rats [20,21]. The dose for lurasidone (0.1 mg/kg) was chosen based on prior NOR studies in C57BL/6J mice which determined the effective dose of lurasidone to restore NOR in subchronic PCP-treated mice [16].

2.3. Drug treatment

For acute drug treatments, rapastinel (1.0 mg/kg, iv), lurasidone (0.1 mg/kg, i.p.) or ketamine (30 mg/kg, ip) were administered 30 min prior to the acquisition trial of the NOR task (described below) to the subchronic ketamine or subchronic PCP-treated animals. For subchronic drug treatments, 7–10 mice/cohort were randomly assigned to Sal, PCP, or ketamine. The Sal-treated mice received 0.9% NaCl; the drug treatment groups received either PCP (10 mg/kg; ip), or ketamine (30 mg/kg; ip) twice daily for 7 days. This was followed by a 7 day washout period during which time, mice were left undisturbed in the home cage until initiation of habituation (see below).

2.4. NOR test

NOR testing in mice was slightly modified from Hashimoto et al. [20] (i.e., size of the box, usage of white background to the walls of the box instead of black reflective surfaces, and duration of the trials) based on preliminary experiments. Our studies showed that when black reflective surfaces were used for the inner surfaces of the NOR box, the animals failed to explore much. Similar observations were made when large objects were used. Hence, we used white walls for the box and small objects for exploration. The dimensions of the NOR box we used for mice is comparable to that of rats. We used box of small dimensions as mentioned by Hashimoto et al. and did not find any significant difference in the object exploration when the dimensions of the NOR box was bigger [20]. We also observed in our preliminary studies, that C57BL/6J mice explored less when the duration of trials were 3 or 5. Hence, we let the animals explore for 10 min in both trials and noticed significant increase in exploration times (unpublished data). Hence we used longer duration of the trials. The NOR apparatus consisted of an open box made of Plexiglas (52 cm L; 52 cm W; 31 cm H) with white walls and a solid floor. The box was positioned approximately 30 cm above the floor, centered on a table such that the overhead lights could not provide a spatial cue. One day after the 7 day washout from subchronic drug treatment or Sal, mice were
habituated to the empty NOR arena, as a group, for one hour, on each of three days prior to the acquisition trial. During the acquisition trial, the mice were allowed to explore two identical objects (e.g., A1 and A2) for 10 min. This was followed by a 24 h inter-trial interval, after which the mice were returned to the home cage. During the retention trial, the mice were allowed to explore the familiar object (A) from the acquisition trial and a novel object (e.g., B). The location of the novel object in the retention trial was randomly assigned for each mouse tested using a pseudorandom schedule. The pseudorandom sequences followed the criteria suggested by Gellerman to reduce the effects of object and place preference [22]. Also, to avoid bias or olfactory trails, we used an objects in triplicates, i.e., that the same object that was used in the acquisition trial was not presented in retention trial. Behavior was recorded on video for blind scoring of object exploration. Object exploration was defined as an animal licking, sniffing, or touching the object with the forepaws while sniffing. The exploration time (s) of each object in each trial was recorded manually by the use of two stopwatches, and if the mice failed to explore for >1(s) in both acquisition and retention trials, they were excluded from the analysis. The discrimination index (DI) [(time spent exploring the novel object—time spent exploring the familiar object)/total exploration time] was then calculated for retention trials.

2.5. Data analysis

All data are expressed as the mean ± S.E.M. (n = 7–10 per group). Exploration data were analyzed by a repeated measures analysis of variance (ANOVA) followed by the pair-wise comparison when a significant effect was detected by the ANOVA. DI data were analyzed by one-way ANOVA followed by Bonferroni test when a significant effect was detected by ANOVA.

3. Results

3.1. Rapastinel prevented acute ketamine-induced NOR deficit in male C57BL/6J mice (experiment 1)

No significant effect on object exploration was found during acquisition trials in any of the groups (F3,31 = 0.90; P = 0.96; data not shown). In the retention trials, there was a significant interaction between drug treatment and object exploration time (F3,31 = 24.76; ***P < 0.001; data not shown). Further post-hoc analysis revealed that wild-type mice given Sal and Sal plus rapastinel (1.0 mg/kg) showed a clear preference for the novel compared to the familiar object, i.e., spent significantly more time exploring the novel versus familiar object (P < 0.001). This effect was abolished in mice treated with acute ketamine (30 mg/kg) — i.e., these mice spent similar amount of time exploring both objects. Furthermore, mice given rapastinel (1.0 mg/kg) prior to acute ketamine (30 mg/kg) showed clear preference for novel compared to familiar objects (P < 0.01). In the DI, there was a significant interaction between the groups (F3,31 = 28.23; ***P < 0.001; Fig. 1). The DI for acute ketamine plus Sal-treated mice was significantly reduced compared to the Sal plus Sal, Sal plus rapastinel, and rapastinel (1.0 mg/kg) plus ketamine (30 mg/kg) treated mice (**P < 0.001; $$$P < 0.001; $$$P < 0.001; Fig. 1). Thus, rapastinel, 1.0 mg/kg significantly prevented the acute ketamine-induced decrease in DI.
3.1. Total exploration times—No significant effect was observed between groups in the total exploration times (acquisition trial + retention trial). Mice from all treatment groups spent almost equal times exploring in the acquisition and retention trials (Sal + Sal = 72.5 ± 5.7; rap + Sal = 76.876.8 ± 3.8; ket + Sal = 82.4 ± 11.0; rap + ket = 79.2 ± 8.3).

3.2. Rapastinel significantly reversed subchronic PCP- and subchronic ketamine-induced NOR deficit in C57BL/6J mice (experiment 2)

No significant effect on object exploration was found during the acquisition trial for any of the groups ($F_{4,47} = 0.76; P = 0.23$; data not shown). In the retention trial, there was a significant interaction between drug treatment and object exploration time ($F_{4,47} = 10.45; ***P < 0.001$; data not shown). Further post-hoc analysis revealed that wild-type mice given Sal showed a clear preference for the novel compared to the familiar object ($P < 0.001$). This effect was abolished in mice treated with subchronic ketamine or subchronic PCP treated animals. Acute rapastinel (1.0 mg/kg) treated animals explored novel object significantly more compared to familiar object, thereby reversing the deficit induced by subchronic PCP or subchronic ketamine ($P < 0.001$; data not shown). In the DI, there was a significant interaction between the groups ($F_{4,47} = 9.30; ***P < 0.001$; Fig. 2). The DI for subchronic PCP- and subchronic ketamine-treated mice was significantly reduced compared to the Sal plus Sal treated control mice (*$P < 0.05$ and **$P < 0.01$; Fig. 2). The DI for subchronic PCP and subchronic ketamine treated animals given rapastinel, 1.0 mg/kg, was significantly increased, thereby significantly showing reversal of NOR impairment produced by both subchronic PCP and subchronic ketamine-treatment (###$P < 0.001$; Fig. 2).

3.2.1. Total exploration times—No significant effect was observed between groups in the total exploration times (acquisition trial + retention trial). Mice from all treatment groups spent almost equal times exploring in the acquisition and retention trials (Sal + Sal = 74.5 ± 5.7; subchronic PCP = 74.8 ± 5.5; subchronic ketamine = 80.3 ± 7.2; subchronic PCP + rapastinel = 73.8 ± 3.8; subchronic ketamine + rapastinel = 86.2 ± 8.3).

3.3. Sub-effective dose rapastinel plus sub-effective dose lurasidone reversed the subchronic ketamine-induced NOR deficit (experiment 3)

No significant effect on object exploration was found during the acquisition trial for any of the groups ($F_{4,43} = 0.92; P = 0.13$; data not shown). In the retention trial, there was a significant interaction between drug treatment and object exploration time ($F_{4,43} = 12.45; ***P < 0.001$; data not shown). Further post-hoc analysis revealed that wild-type mice given Sal showed a clear preference for the novel compared to the familiar object ($P < 0.001$). This effect was abolished in mice treated with subchronic ketamine and in animals given subchronic ketamine plus sub-effective dose rapastinel (0.3 mg/kg) and subchronic ketamine plus sub-effective dose lurasidone (0.1 mg/kg). However, when the subchronic ketamine was given sub-effective dose lurasidone plus sub-effective dose rapastinel, the animals explored the novel object significantly more compared to the familiar object ($P < 0.001$; data not shown). The DI showed a significant interaction between groups ($F_{4,43} = 10.04; ***P < 0.001$; Fig. 3). Subchronic ketamine plus Sal-, subchronic ketamine plus rapastinel (0.3 mg/kg)-, and subchronic ketamine plus lurasidone (0.1 mg/kg)-treated mice showed significant reductions in the DI compared to saline controls (###$P < 0.001$). The combination of sub-
effective dose rapastinel (0.3 mg/kg) plus sub-effective dose lurasidone (0.1 mg/kg) significantly reversed the decrease in the DI produced by subchronic ketamine (###P < 0.001; Fig. 3). The effect of the combination of sub-effective dose rapastinel and lurasidone was not significantly different from that of the effective doses of either drug, given alone.

3.3.1. Total exploration times—No significant effect was observed between groups in the total exploration times (acquisition trial + retention trial). Mice from all treatment groups spent almost equal times exploring in the acquisition and retention trials (Sal + Sal = 77.5 ± 6.7; subchronic ketamine = 86.3 ± 5.2; subchronic ketamine + subeffective dose rapastinel = 73.2 ± 4.7; subchronic ketamine + subeffective dose lurasidone = 71.5 ± 6.2; subchronic ketamine + subeffective dose rapastinel + subeffective dose lurasidone = 78.5 ± 5.1

4. Discussion

The major findings of this study strongly suggest that rapastinel, an NMDAR glycine site functional partial agonist, (i) did not induce NOR deficit; (ii) significantly prevented acute ketamine-induced NOR deficit and reversed the deficit in NOR produced by subchronic administration of the NMDAR antagonists, ketamine and PCP; and (iii) when administered at sub-effective dose, combined with antipsychotic/antidepressant sub-effective dose lurasidone restored NOR in subchronic ketamine-treated mice.

These results suggest that rapastinel differs from the effects of NMDAR non-competitive antagonists such as PCP, ketamine, and dizocilpine (MK-801) in not impairing NOR in mice. Ketamine has been reported to be a rapidly active antidepressant, able to diminish suicidal ideation and planning [6-8]. Rapastinel has also been shown to be significantly effective in improving depression in a proportion of patients who did not adequately respond to prior treatments for depression, including electroconvulsive treatment [2]. There is no data comparing ketamine and rapastinel in clinical trials, so their relative efficacy for this critically important indication is unknown. As many patients with major or bipolar depression who are potentially in need of rapidly acting antidepressant drugs are known to have clinically significant cognitive impairment [23,24], it is important to determine if there are differences between ketamine and rapastinel in their effect on cognition, as well as psychopathology in patients. A subset of depressed patients, e.g., those with unipolar or bipolar depression with psychotic features are also prone to experience psychosis [25]. Thus, some patients with mood disorders may be at higher risk for additional cognitive impairment or recurrence of psychosis from ketamine than from rapastinel, even with a single treatment, as the adverse effects of ketamine on cognition and psychopathology may emerge from a single administration at doses comparable to those which are required to treat depression. With multiple administrations of ketamine for persistent, recurrent treatment of resistant depression, as has been sometimes been done with ketamine, the risk for cognitive impairment and psychosis could be higher [26]. The finding that sub-effective dose rapastinel (0.3 mg/kg) potentiated sub-effective dose of multi-receptor AAPD/antidepressant drug lurasidone (0.1 mg/kg), is clinically relevant, as some patients treated with lurasidone or other AAPDs may be treated with rapastinel. It is possible that atypical AAPDs such as lurasidone, could reduce the risk for cognitive impairment and psychosis in treatment-resistant depressed patients given a ketamine trial.
The ketamine- and PCP-induced deficits in rodent NOR is likely due to the disruption of synaptic function and plasticity [27,28]. Therefore, the ability of rapastinel to prevent and reverse the effects of ketamine and PCP to cause deficits in NOR may result from facilitation of NMDAR- and GABAergic-dependent synaptic plasticity in hippocampus [28], perirhinal and entorhinal cortices, and medial prefrontal cortex and preservation of, or restoration, of functional integration of these critical brain areas for learning and memory [29]. In rat hippocampal slices, rapastinel preferentially enhanced conductance of GluN2B-containing NMDARs at the Schaffer collateral-CA1 synapses in vitro [30], and also enhanced the magnitude of long-term potentiation (LTP) of synaptic transmission while simultaneously reducing that of long-term depression (LTD) [30,31]. These effects would be expected to have a pro-cognitive benefit.

Both ketamine and PCP have been shown to bind selectively to GluN2B-containing NMDARs in cells transfected with GluNR1A/2B NMDARs. Also, GluN2B overexpression has been shown to improve the performance of adult rats in object recognition task at longer inter-trial intervals [32]. Further, KIF17 knock-out mice, which have reduced synaptic GluN2B levels showed significant impairment in object recognition task at longer inter-trial intervals [33]. It has been reported that in vivo administration of lurasidone produced a significant and selective enhancement of NMDAR-mediated synaptic responses and surface expression of GluN2A and GluN2B subunits [34]. Since rapastinel also preferentially modulates GluN2B subunits, it is possible that the basis for the efficacy of the combination of sub-effective doses of both lurasidone and rapastinel to restore NOR in the subchronic ketamine-treated mice is enhancement of GluN2B subunits in receptor function. The finding that sub-effective dose rapastinel (0.3 mg/kg) potentiated sub-effective dose of multi-receptor AAPD/antidepressant drug lurasidone (0.1 mg/kg), is clinically relevant as some patients treated with lurasidone or other AAPDs may be treated with rapastinel.

In animal studies, rapastinel enhanced performance in a variety of hippocampal-dependent learning tasks, including trace eye blink conditioning and the Morris water maze, in both young adult and learning-impaired aging rats [31], and facilitated mPFC-dependent positive emotional learning [35]. On the other hand, acute ketamine administration in both normal rats [36] and mice induces a deficit in NOR; the latter was reversed by a selective mGluR5 agonist, \((RS)-2\text{-chloro-5-hydroxyphenylglycine (CHPG) [37]. Also, in agreement with the results reported here, subchronic ketamine induces a significant deficit in working memory span capacity in an odor span task [21] in rats.}

5. Conclusions

These findings demonstrate that rapastinel differs from ketamine in not producing impairment in NOR in mice and can prevent impairment in NOR produced by acute or subchronic ketamine. Clinical studies are needed to determine if these differences between ketamine and rapastinel in mice are clinically relevant. Since drugs such as lurasidone which are ameliorative in the subchronic NMDAR-model of cognitive impairment in schizophrenia are also effective to improve cognitive impairment in some patients with schizophrenia [38,39], clinical study is indicated to determine if rapastinel may also have some direct cognitive benefits in patients with schizophrenia or mood disorders.
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Abbreviations

5-HT       serotonin
AAPD      atypical antipsychotic drugs
CHPG       (RS)-2-chloro-5-hydroxyphenylglycine
CI         cognitive impairing
CIS        cognitive impairment associated in schizophrenia
DA         dopamine
DI         discrimination index
GABA       gamma amino butyric acid
Ket        ketamine
LTD        long-term depression
LTP        long-term potentiation
NMDAR      N-methyl-D-aspartate receptor
NOR        novel object recognition
GluN2A      NMDR 2-subunit A
GluN2B      NMDR 2-subunit B
PCP         phencyclidine
Sal         saline
WT          wild-type

References


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GLYX-13 (rapastinel), a putative fast-acting anti-depressant, was effective in reversing subchronic phencyclidine (PCP)- and ketamine-induced persistent deficits in novel object recognition (NOR) task in mice.

Acute ketamine, but not rapastinel, caused a transient NOR deficit, which was prevented by pretreatment with rapastinel.

Rapastinel potentiated the ability of a sub-effective dose of lurasidone, an atypical antipsychotic drug with antidepressant properties, to restore NOR in subchronic ketamine-treated mice.

The differences in rapastinel and ketamine on this type of cognitive function in mice are noteworthy and may be relevant to safety issues in man.
Fig. 1.  
The effect of saline (Sal; 0.9%; iv), acute rapastinel (rap; 1.0 mg/kg; iv), acute ketamine (ket; 30 mg/kg; ip); rap + ket (1.0 mg/kg + 30 mg/kg) in an NOR task in male C57BL/6J mice. Data are expressed as mean ± S.E.M. (N = 7–10 per group). DI, ***P < 0.001; significant reduction in DI compared to sal; ###P < 0.001; significant reduction in DI compared to rap + Sal; $$$P<0.001; significant increase in DI compared to ket + sal.
Fig. 2.
The effect of subchronic sal (0.9%), subchronic PCP and subchronic ket (10 and 30 mg/kg; ip; bid; 7 days; 7 days washout); subchronic PCP + rap (1.0 mg/kg), and subchronic ket + rap (1.0 mg/kg) in an NOR task in male C57BL/6J mice. Data are expressed as mean ± S.E.M. (N = 7–10 per group). DI, *P < 0.05; **P < 0.01; significant reduction in DI compared to Sal treatment. ###P < 0.001; significant increase in DI in subchronic PCP- and subchronic ket-treated mice given rap (1.0 mg/kg) compared to subchronic PCP + Sal or subchronic ket + Sal.
Fig. 3.
The effect of subchronic Sal (0.9%), subchronic ket (30 mg/kg), subchronic ket + rap(0.3 mg/kg; sub-effective dose), subchronic ket + lurasidone (0.1 mg/kg; lur; sub-effective dose), subchronic ket + sub-effective dose rap + sub-effective dose lur in an NOR task in male C57BL/6J mice. Data are expressed as mean ± S.E.M. (N = 8–10 per group). DI, ***P < 0.001; significant reduction in DI compared to Sal-treated mice. ###P < 0.001: Significant increase in DI compared to subchronic ket + Sal; subchronic ket + sub-effective dose rap; subchronic ket + sub-effective dose lur.