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A Single Post-extinction Dose of Ifenprodil Does Not Detectably Alter Contextual Fear in Rats Exposed to Single Prolonged Stress: A Pilot Dose-Ranging Study

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Abstract

Introduction

Ifenprodil, a clinically available antagonist selective for GluN2B-containing N-methyl-D-aspartate (NMDA) receptors, has been examined in small clinical studies of posttraumatic stress disorder (PTSD). Because GluN2B-containing receptors contribute to extinction learning, we asked whether a single dose of ifenprodil, given immediately after an extinction session, alters contextual fear at the next session in rats exposed to single prolonged stress (SPS), a rodent model of PTSD.

Methods

Male Sprague-Dawley rats were exposed to SPS and, seven days later, to contextual fear conditioning, followed by extinction sessions on three consecutive days (EX-1 to EX-3). Ifenprodil (10, 25, or 50 mg/kg, intraperitoneally; n = 6 per dose) or saline (n = 10) was injected once, immediately after EX-2. Freezing was scored automatically, and freezing at EX-3 was the outcome of interest. The saline group and the ifenprodil groups were tested as separate batches, so treatment was confounded with batch.

Results

Freezing before treatment was similar across groups. At EX-3, freezing did not differ between the saline and ifenprodil groups ($F(3, 24) = 0.34$, $p = 0.80$), and the result was unchanged after adjustment for freezing at EX-2. The course of freezing across the three sessions did not differ between groups. Freezing increased from EX-2 to EX-3 after 50 mg/kg, but this change did not differ significantly from that after saline.

Conclusions

In male rats exposed to SPS, a single post-extinction dose of ifenprodil of up to 50 mg/kg did not detectably alter contextual fear at the next extinction session. Because treatment was confounded with batch and the groups were small, these findings are preliminary and hypothesis-generating. Larger studies with treatments distributed within each batch are needed to detect effects of moderate size.

Categories: Neurology, Psychiatry, Pharmacology
Keywords: contextual fear conditioning, fear extinction, glun2b, ifenprodil, memory consolidation, nmda receptor, posttraumatic stress disorder, rat model, single prolonged stress

Introduction

Posttraumatic stress disorder (PTSD) develops in a subset of individuals exposed to traumatic events. Trauma-focused psychotherapies based on exposure are effective, but a substantial proportion of patients retain clinically significant symptoms after treatment [1,2]. Exposure therapy is thought to engage fear extinction, a form of new inhibitory learning that competes with, rather than erases, the original fear memory [3,4]. Drugs that modify the consolidation of extinction memory are therefore candidate adjuncts to exposure-based treatment.

Glutamatergic dysregulation has been implicated in PTSD [5], and N-methyl-D-aspartate (NMDA) receptors containing the GluN2B subunit participate in extinction learning. GluN2B antagonism in the lateral amygdala impaired the acquisition of extinction [6], GluN2B-containing receptors in the amygdala contribute to the extinction of conditioned fear [7], and ifenprodil infused into the hippocampus immediately after extinction training impaired contextual fear extinction in rats [8]. Single prolonged stress (SPS), a well-characterized rodent model of PTSD [9-11], impairs contextual fear extinction and increases hippocampal NMDA receptor subunit expression [12]. Whether GluN2B-dependent consolidation of extinction is preserved after such severe stress is not known.

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Ifenprodil is an antagonist selective for GluN2B-containing NMDA receptors [13] that is approved in Japan for dizziness associated with the sequelae of cerebrovascular disease. Case reports described reduced flashbacks during ifenprodil treatment in patients with PTSD [14,15], and a small placebo-controlled trial in adolescents with PTSD reported improvement in some secondary outcomes [16]. To our knowledge, the effect of systemic ifenprodil given after extinction training has not been reported in an animal model of PTSD. In this pilot dose-ranging study, we examined whether a single dose of ifenprodil given immediately after an extinction session alters contextual fear at the next session in male rats exposed to SPS; freezing at the third extinction session (EX-3) was the outcome of interest. Ifenprodil was given systemically, by a route analogous to its clinical use, rather than into a target structure, so that the result would bear on whether a drug already available to patients can modify the consolidation of extinction. The doses were chosen to span a fivefold range for this pilot study; they were not selected on the basis of measured receptor occupancy, and whether they produced meaningful GluN2B blockade in the relevant structures during the consolidation window is not established by these data.

Materials And Methods

Ethics statement

All procedures were approved by the Animal Experiment Committee of Sanyo-Onoda City University (approval number 2024-45-A) and complied with the institutional guidelines for the care and use of laboratory animals. The study is reported in accordance with the ARRIVE 2.0 guidelines [17]. At the end of the experiment, rats were euthanized by isoflurane overdose followed by cervical dislocation.

Animals

Male Sprague-Dawley rats (Slc:SD; Japan SLC, Shizuoka, Japan) were housed one or two per cage with food (CE-2; CLEA Japan, Tokyo, Japan) and water available ad libitum, under a 12-hour light/dark cycle (lights on at 08:00) at 23 ± 3°C and 50 ± 10% relative humidity. Rats in the ifenprodil groups were 5-6 weeks of age on arrival and were exposed to SPS approximately one week after arrival. Each rat was weighed on the dosing day, and the injection volume was calculated from its body weight. The experimental unit was the individual rat. All behavioral testing took place during the light phase. Only male rats were studied. SPS was developed and characterized in male rats [9], and this experiment was designed to be comparable with that work; because stress and extinction responses may differ between sexes, the present findings cannot be generalized to females.

Study design and allocation

This pilot dose-ranging study comprised four groups of SPS-exposed rats that received a single intraperitoneal injection of saline (n = 10) or ifenprodil at 10, 25, or 50 mg/kg (n = 6 each) immediately after the second extinction session (Figure *1*). Each group was tested as a separate batch: the saline group in April and May 2024 and the ifenprodil groups between November 2024 and January 2025, all in the same laboratory under the same approved protocol, with the same schedule of SPS, conditioning, extinction, and injection, the same apparatus, and automated freezing scoring. The group size of six rats per dose followed the approved protocol; no formal sample-size calculation was performed. The saline group had been completed under the same approved protocol before testing of the ifenprodil groups began; animals could therefore not be randomized to treatment within a batch, and the experimenters were aware of the treatment for each batch. Treatment is consequently completely confounded with batch and with the period of testing. This confounding cannot be removed by statistical adjustment, and all between-group comparisons reported here are exploratory. All rats tested were included in the analysis.

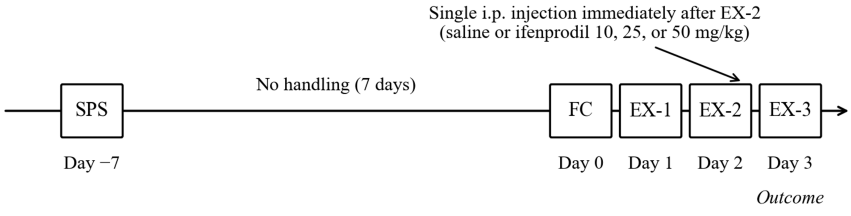


FIGURE 1: Experimental timeline

Rats were exposed to single prolonged stress (SPS) on Day −7 and left undisturbed for seven days. Contextual fear conditioning (FC) was performed on Day 0 and extinction sessions (EX-1 to EX-3) on Days 1-3. A single intraperitoneal injection of saline or ifenprodil (10, 25, or 50 mg/kg) was given immediately after EX-2, and freezing at EX-3 was the outcome of interest.

Single prolonged stress

SPS was induced as described previously [9,10], with isoflurane substituted for diethyl ether. Rats were restrained for two hours, immediately subjected to 20 minutes of forced swimming in water at room temperature (depth 300 mm), allowed to rest for 10 minutes, and then exposed to isoflurane (FUJIFILM Wako Pure Chemical, Osaka, Japan; 3%, approximately five minutes) until loss of consciousness. Rats were then left undisturbed for seven days.

Contextual fear conditioning and extinction

Conditioning and extinction took place in a square chamber with a grid floor inside a sound-attenuating enclosure, under constant illumination, with the chamber wiped with alcohol between rats; footshocks were delivered with a shock generator (LE100-26; Panlab, Barcelona, Spain). Seven days after SPS (Day 0), rats received two footshocks (0.8 mA, four seconds each) after a five-minute habituation period. On Days 1-3, rats were re-exposed to the chamber without footshock for 6.5 minutes (extinction sessions EX-1 to EX-3). Freezing was scored with video-tracking software (SMART 3.0; Panlab/Harvard Apparatus, Barcelona, Spain) over a 300-second window beginning 90 seconds after placement in the chamber, as in the laboratory's standard procedure, and was expressed as total freezing time (seconds). Freezing was scored only by the automated system; no sessions were rescored manually, so the agreement between the automated measure and observer scoring was not established in this experiment.

Drug treatment

Ifenprodil tartrate (Selleck Biotechnology, Tokyo, Japan) was prepared at 8.33 mg/mL in 0.5% (w/v) sodium carboxymethylcellulose in physiological saline and injected intraperitoneally at 1.2, 3, or 6 mL/kg for 10, 25, or 50 mg/kg, respectively (doses expressed as the tartrate salt). Rats in the saline group received physiological saline (0.9%). All injections were given once, immediately after EX-2, so that the drug was present during the consolidation of the second extinction session but not during EX-3. The control animals therefore received physiological saline rather than the 0.5% carboxymethylcellulose vehicle used for ifenprodil, so the study included no vehicle-matched control. Because the drug concentration was fixed, the injection volume, and with it the amount of carboxymethylcellulose administered, increased with dose among the ifenprodil groups (1.2 to 6 mL/kg). Any comparison between the saline group and an ifenprodil group therefore carries a difference in vehicle, and any comparison between doses carries a difference in injection volume. Plasma and brain concentrations of ifenprodil were not measured.

Statistical analysis

Freezing at EX-1, EX-2, and EX-3 and the change from EX-2 to EX-3 were compared among the four groups by one-way analysis of variance (ANOVA); freezing at EX-3 was also analyzed by analysis of covariance with freezing at EX-2 as the covariate. Freezing across the three sessions was analyzed by two-way mixed ANOVA (group × session) with Greenhouse-Geisser correction. Effect sizes for F tests were expressed as η^2 (one-way ANOVA) or partial η^2 (analysis of covariance and mixed ANOVA). Each ifenprodil dose was compared with saline by Welch's t-test, with mean differences, 95% confidence intervals (CIs), and Hedges' g; these comparisons were not adjusted for multiplicity. Tests were two-tailed with $\alpha = 0.05$, and data are presented as mean ± standard error of the mean (SEM). Analyses were performed in Python 3.14 with pingouin 0.6.1 [18], statsmodels 0.14.6 [19], and SciPy 1.17.1 [20]. Pairwise comparisons were not adjusted for multiplicity, so the intervals reported for them are not simultaneous, and no statistical procedure can separate treatment from batch in this design. The analyses are therefore descriptive, and the interpretation rests on the estimates and their CIs rather than on the results of significance tests.

Results

All 28 rats completed conditioning and the three extinction sessions and were included in the analysis (saline, n = 10; each ifenprodil dose, n = 6). Body weights recorded on the dosing day ranged from 224 to 271 g in the 10 and 50 mg/kg groups. Drug concentrations were not measured.

Before treatment, conditioned fear was robust in all groups: at EX-1, mean freezing was about three-quarters or more of the scored window in every group, and freezing at EX-1 and EX-2 did not differ between groups (Figure *2A*, Tables *1*, *2*). The groups therefore entered treatment with comparable measured levels of conditioned fear. Similar pre-treatment freezing, however, does not rule out differences between the groups in factors that were not measured, and it should not be taken as evidence that the groups were otherwise equivalent.

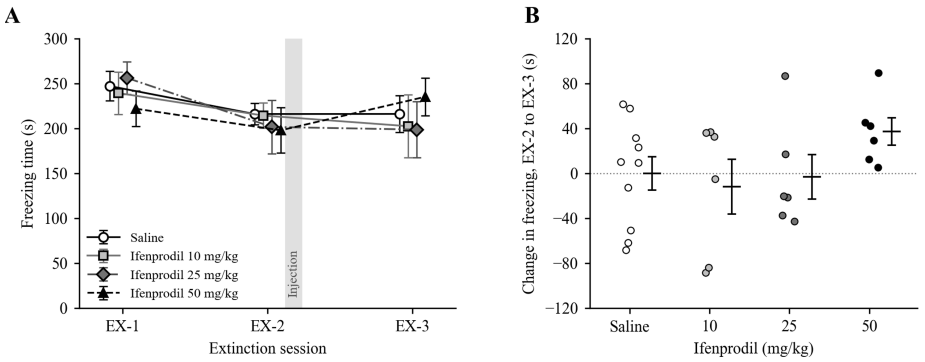


FIGURE 2: Freezing before and after a single post-extinction dose of ifenprodil

(A) Freezing time (seconds) in extinction sessions EX-1 to EX-3; mean ± SEM. Saline, n = 10; ifenprodil 10, 25, and 50 mg/kg, n = 6 each. The shaded bar indicates the single intraperitoneal injection given immediately after EX-2. (B) Change in freezing from EX-2 to EX-3 in individual rats; horizontal bars indicate mean ± SEM; panel B shows every animal tested. Statistical results are given in Table 2. The scored window was 300 seconds.

Group (n)	EX-1, s	EX-2, s	EX-3, s	Change, EX-2 to EX-3, s
Saline (10)	247.2 ± 16.4 (51.9)	216.1 ± 12.0 (37.9)	216.2 ± 20.4 (64.4)	0.1 ± 14.9 (47.2)
Ifenprodil 10 mg/kg (6)	239.5 ± 23.5 (57.6)	214.4 ± 14.1 (34.5)	202.6 ± 34.9 (85.4)	−11.9 ± 24.3 (59.6)
Ifenprodil 25 mg/kg (6)	256.2 ± 18.1 (44.2)	201.7 ± 29.8 (73.1)	198.8 ± 31.1 (76.3)	−3.0 ± 19.9 (48.7)
Ifenprodil 50 mg/kg (6)	222.0 ± 19.9 (48.7)	198.0 ± 25.2 (61.7)	235.3 ± 20.9 (51.3)	37.4 ± 12.2 (30.0)

TABLE 1: Freezing in each extinction session

Values are mean ± SEM, with the standard deviation in parentheses. The scored window was 300 seconds.

Outcome and comparison	Statistical test	Test statistic	df	p-value	Effect size	Mean difference, s	95% CI, s
EX-1: four groups	One-way ANOVA	F = 0.50	3, 24	0.68	$\eta^2 = 0.06$	–	–
EX-2: four groups	One-way ANOVA	F = 0.21	3, 24	0.89	$\eta^2 = 0.03$	–	–
EX-3: four groups	One-way ANOVA	F = 0.34	3, 24	0.80	$\eta^2 = 0.04$	–	–
EX-3 adjusted for EX-2: group	ANCOVA	F = 1.19	3, 23	0.34	Partial $\eta^2 = 0.13$	–	–
Change, EX-2 to EX-3: four groups	One-way ANOVA	F = 1.27	3, 24	0.31	$\eta^2 = 0.14$	–	–
EX-1 to EX-3: session	Mixed ANOVA	F = 7.29	2, 48	0.002	Partial $\eta^2 = 0.23$	–	–
EX-1 to EX-3: group	Mixed ANOVA	F = 0.05	3, 24	0.98	Partial $\eta^2 = 0.01$	–	–
EX-1 to EX-3: group × session	Mixed ANOVA	F = 1.26	6, 48	0.29	Partial $\eta^2 = 0.14$	–	–
EX-3: 10 mg/kg vs. saline	Welch's t-test	t = −0.34	8.4	0.74	g = −0.18	−13.6	−105.9 to 78.6
EX-3: 25 mg/kg vs. saline	Welch's t-test	t = −0.47	9.3	0.65	g = −0.24	−17.4	−101.2 to 66.4
EX-3: 50 mg/kg vs. saline	Welch's t-test	t = 0.66	12.6	0.52	g = 0.30	19.1	−44.1 to 82.4
Change: 10 mg/kg vs. saline	Welch's t-test	t = −0.42	8.8	0.69	g = −0.22	−12.0	−76.8 to 52.9
Change: 25 mg/kg vs. saline	Welch's t-test	t = −0.12	10.4	0.91	g = −0.06	−3.0	−58.2 to 52.1
Change: 50 mg/kg vs. saline	Welch's t-test	t = 1.93	13.9	0.074	g = 0.84	37.3	−4.1 to 78.7

TABLE 2: Statistical tests

Mean differences are ifenprodil − saline; pairwise comparisons were not adjusted for multiplicity. Confidence intervals are wide throughout, and the intervals for all comparisons include zero. For the session and group × session effects, p-values are Greenhouse-Geisser corrected (ε = 0.96). A dash indicates not applicable.

ANCOVA, analysis of covariance; ANOVA, analysis of variance; CI, confidence interval; df, degrees of freedom; g, Hedges' g.

After treatment, freezing at EX-3 did not differ between the saline group and any ifenprodil group, and this result was unchanged when freezing at EX-2 was taken into account (Table *2*). Across the three sessions, freezing declined modestly overall, and the course of freezing did not differ between groups (Figure *2A*, Table *2*).

The change in freezing from EX-2 to EX-3 is shown for individual rats in Figure *2B*. On average, freezing was unchanged in the saline group and changed little after 10 or 25 mg/kg. After 50 mg/kg, freezing increased in all six rats; this was the largest mean change among the doses, but the difference from saline was 37.3 seconds (95% CI, -4.1 to 78.7 seconds), an interval that includes zero and spans values ranging from negligible to large (Table *2*). This increase is an exploratory observation; it does not establish a pharmacological effect and cannot be separated from the batch in which it was obtained.

Discussion

In this pilot dose-ranging study, a single dose of ifenprodil given immediately after an extinction session did not detectably alter contextual fear at the next session in rats exposed to SPS. The groups began treatment with comparable levels of conditioned fear, and neither freezing at EX-3, with or without adjustment for freezing at EX-2, nor the course of freezing across the three sessions differed between the saline and ifenprodil groups.

In non-stressed rats, GluN2B antagonism impaired extinction when given into the lateral amygdala before extinction training [6] and when ifenprodil was infused into the hippocampus after training [8]. The present study differed from these reports in that ifenprodil was given systemically, the rats had been exposed to SPS, and freezing remained high across the three sessions. The rise in freezing after 50 mg/kg is in the direction expected if consolidation of extinction had been impaired, but it was small relative to the variation between rats and was not seen at the lower doses. The following explanations are hypothesis-generating rather than conclusions. Plasma and brain concentrations of ifenprodil were not measured, so the degree and duration of GluN2B blockade achieved during the consolidation window are unknown, and no explanation offered here can be distinguished from the others based on the present data. Systemic administration may not have produced sufficient receptor blockade in the relevant circuits during the consolidation window, and the high level of freezing in all groups left limited room to detect a further impairment. It is also possible that extinction after severe stress, which is itself impaired in this model [12], depends less on the GluN2B-mediated processes described in non-stressed animals; this possibility remains to be tested.

The most fundamental limitation of this study is not its size. Each treatment was tested as a separate batch, so that any difference between the groups reflects the treatment, the batch, and the period of testing together, and these cannot be separated; the comparisons are therefore exploratory, and no adjustment can repair this. Distributing treatments within each batch, with randomization to treatment inside the batch, would remove this confounding in future studies. The saline group received physiological saline rather than the carboxymethylcellulose vehicle used for ifenprodil, so the study had no vehicle-matched control, and, because the drug concentration was fixed, the injection volume, and with it the amount of carboxymethylcellulose administered, increased with dose among the ifenprodil groups. A vehicle-matched control and a fixed injection volume would remove these differences. Group sizes were also small, so the estimates are imprecise: effects of moderate size, and in some comparisons large ones, remain compatible with these data, and the absence of a significant difference should not be read as evidence of no effect [21]. The estimates reported here, with their CIs, are intended to inform the planning of larger studies. The study did not include an SPS-unexposed group, so the extinction deficit reported for this model was not verified in these animals; drug concentrations were not measured, so the degree of GluN2B blockade achieved is unknown; the automated scoring was not validated against manual scoring in this experiment; the pairwise comparisons were not adjusted for multiplicity, so the intervals reported for them are not simultaneous; and only male rats were studied. Reporting such results nevertheless helps to limit the publication bias that can inflate the apparent efficacy of interventions in animal studies [22].

Conclusions

In male rats exposed to SPS, a single dose of ifenprodil given immediately after an extinction session did not detectably alter contextual fear at the next session at any of the doses tested. The increase in freezing at the highest dose was in the direction expected from impaired consolidation of extinction, but the estimate was imprecise and did not establish a pharmacological effect. Because treatment was completely confounded with batch and the uncertainty about the difference at the highest dose was large, these findings are preliminary and hypothesis-generating, and they do not provide evidence against a role for GluN2B-containing receptors in the consolidation of extinction.

Studies with larger groups, randomization to treatment within each batch, a vehicle-matched control with a constant injection volume, subjects of both sexes, and measurement of drug exposure will be needed to determine whether post-extinction GluN2B antagonism modifies the extinction of fear after severe stress.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Hidenori Sagara, Kyosuke Nagura

Acquisition, analysis, or interpretation of data: Hidenori Sagara, Kyosuke Nagura, Minami Hamada

Drafting of the manuscript: Hidenori Sagara

Critical review of the manuscript for important intellectual content: Hidenori Sagara, Kyosuke Nagura, Minami Hamada

Supervision: Hidenori Sagara

Disclosures

Human subjects: All authors have confirmed that this study did not involve human participants or tissue.
Animal subjects: The Animal Experiment Committee of Sanyo-Onoda City University issued protocol

number 2024-45-A. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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