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Original Article

An Assessment of the Antidepressant Potential of Deramciclane in Two Animal Tests

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Abstract

Background and objectives: Preclinical studies of the serotonin 2A (5-HT2A) antagonist deramciclane suggested an anxiolytic profile, which has not been unequivocally established in the clinic. The same receptor profile also indicated that the compound may exhibit antidepressant potential. However, evidence for these effects remains inconclusive. The present study examined the effect of the drug in two preclinical tests with predictive validity for antidepressant activity.

Methods: The antidepressant-like activity of deramciclane was assessed in male Sprague-Dawley rats by measuring immobility time in the forced swim test (doses: 1, 5 mg/kg) and ambulation scores in the bilateral olfactory bulbectomized (doses: 5, 10 mg/kg) rat model. In both tests, the clinically effective antidepressant imipramine served as the control condition.

Results: In the forced swim test, there was a statistically significant effect of treatment on immobility time ($F_{2,34} = 5.77$; $p < 0.01$; analysis of variance), which was attributable to the effect of the 5 mg/kg dose ($p < 0.01$; Bonferroni post-hoc test). Deramciclane at 1 mg/kg was not significantly different from vehicle-treated animals. By contrast, neither dose of deramciclane (5 mg/kg or 10 mg/kg) reversed the hyperactivity of olfactory bulbectomized rats, whereas imipramine was active in both tests.

Conclusions: Deramciclane demonstrates contradictory evidence for antidepressant-like activity in two validated pharmacological tools that identify such potential. The agent is clearly active in the forced swim test but not in the bulbectomized rat model. Further evaluation of the antidepressant-like potential of deramciclane in pharmacological models with predictive validity is warranted, and a more detailed examination of the dose-response relationship may be informative.

Introduction

Deramciclane (EGIS-3886; N, N-dimethyl-2-[[(1R,2S,4R)-1,7,7-trimethyl-2-phenyl-2-bicyclo[2.2.1]heptanyl]oxy]ethanamine) is a psychoactive compound originally investigated for its anxiolytic activity.[1] Although deramciclane showed promising anxiolytic-like effects across a range of preclinical assays, including Vogel's test, social interaction test, marble-burying behavior, and light-dark box,[1] it failed to separate from placebo in a combined analysis of Phase III trials in generalized anxiety disorder and was not brought to market.[2] Pharmacologically, the drug exhibits high affinity for serotonin 2A (5-HT2A) receptors as an antagonist and partial agonist activity at 5-HT2C receptors.[3] Additional pharmacological activities include inhibition of high affinity synaptosomal [^{3}H]-gamma-aminobutyric acid (GABA) reuptake, high affinity for sigma receptors, and low to moderate affinity for dopamine D1 and D2 receptors, as well as histamine H1 receptors.[4] The drug also demonstrated anticonvulsant activity in preclinical testing,[1] but was reported to lack antidepressant activity in some pharmacological predictive models.[4]

Given the putative role of serotonin receptors in the aetiology of major depression and the activity of effective antidepressants at various members of the serotonin receptor family, the lack of activity of deramciclane in preclinical tests seems paradoxical.[5] While much focus has been placed on presynaptic 5-HT1A receptor activity in mediating antidepressant effects, particularly for serotonin reuptake inhibitors, several observations suggest an equally important role for 5-HT2A receptors in both the etiology of depression and the mechanism of action of antidepressant medications.[6] Upregulated 5-HT2A receptors have been measured in the frontal cortex from postmortem brain tissue of unmedicated individuals with depression, potentially

Keywords: Behavioral pharmacology; Deramciclane; Forced swim test; Olfactory bulbectomy; 5HT2A receptor; Antidepressant-like activity; 5HT1A receptor activity.
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implicating these receptors in the pathophysiology of the disorder.[7] Furthermore, these receptors are implicated in antidepressant drug action, with some antidepressants, such as mirtazapine, augmenting antidepressant response via 5-HT2A receptor antagonism.[8] The potent 5-HT2A antagonists trazodone and nefazodone are both clinically effective antidepressant agents.[9,10] Antidepressant treatment, including electroconvulsive therapy, can lead to downregulation of 5-HT2A receptors, which has been associated with improved mood and reduced anxiety in some individuals.[6,11] Moreover, 5-HT2A receptors may be involved in neurogenesis, a process thought to be important for antidepressant action.[12] Interactions of 5-HT2A receptors occur with other neurotransmitter systems, such as GABAergic and glutamatergic systems, which are also implicated in depression. Activation of 5-HT2A receptors in the anterior cingulate cortex can increase the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/N-methyl-d-aspartate (NMDA) glutamatergic transmission ratio, which may be reduced in depressive and anxiety disorders.[13]

Receptors of the 5-HT2A subtype are a key focus in the understanding and treatment of major depressive disorder. They are implicated in the pathophysiology of depression, the mechanism of action of certain antidepressants, and the process of neurogenesis. Therefore, the present study aimed to evaluate the hypothesis that deramciclane possesses antidepressant-like properties, using two well-validated preclinical models: the forced swim test and the olfactory bulbectomy paradigm.

Materials and methods

Animals and accommodation

Male Sprague-Dawley rats weighing approximately 200 g upon arrival were purchased from Specific Pathogen Free Laboratories, Perth, Western Australia, and used in the study. On arrival, animals were housed four per cage in square, hard-bottomed polypropylene cages measuring 40 × 20 × 20 cm, fitted with metal grid lids. Animals were provided with sawdust for bedding and shredded paper for nesting and maintained on a 12:12 h light–dark cycle (lights on at 0800 h) with ad libitum access to standard rat chow and water. Room temperature was maintained at 22 ± 1°C throughout the study. One week before behavioral testing, all animals were weighed and handled daily by the experimenter. Animals were assigned to treatment groups to ensure comparable average weights between groups. Animal care and experimental procedures were conducted in accordance with the NHMRC/CSIRO/AEC Australian Code of Practice for the Care and Use of Animals for Scientific Purposes. The study was approved by the Austin Health Animal Ethics Committee (Approval Numbers A2000/00888 and A2005/02254). Following completion of behavioral testing, all rats were euthanized according to ethical guidelines. The Forced Swim Test was conducted prior to the release of the NHMRC "Statement on the Forced Swim Test in Rodent Models" issued on 24 January 2024. Separate groups of animals were used for the forced swim test and the olfactory bulbectomy experiments.

Drugs and chemicals

Deramciclane fumarate was provided as a gift from Egis Pharmaceuticals (Budapest, Hungary) and used as received. Imipramine hydrochloride, dimethyl sulfoxide, and hydroxyethyl cellulose were purchased from Sigma-Aldrich (Sydney, Australia). 8-OH-DPAT (8-Hydroxy-2-(di-n-propylamino)tetralin) was purchased from Sapphire Biosciences (Sydney, Australia).

Experiment 1: Forced swim test

The forced swim test is a putative assay of "behavioral despair".[14] Briefly, rats were gently placed in individual plexiglass cylinders (height, 60 cm; diameter, 20 cm) containing water 30 cm deep at 25°C. Behavioral testing commenced at 1000 h. Rats were initially exposed to the cylinder for a 15-min "pretest session", after which they were removed, dried, and returned to fresh bedding in their home cages. Fifteen minutes following removal from the water, each rat received an intraperitoneal injection of deramciclane (1 mg/kg or 5 mg/kg) or vehicle (dimethyl sulfoxide). Drugs were administered in a volume of 1 ml/kg. Each treatment group comprised 12 animals. Rats were re-exposed to the swimming condition in a similar environment for 5 min, 24 h after the first exposure. At 5 h and 1 h before the second exposure, animals received the test substances. Following the second swim session, animals were dried and returned to fresh bedding in their home cages. The primary behavioral outcome measured was the duration of immobility during the second swim session. A reduction in immobility time was interpreted as indicative of antidepressant-like behavior. Both typical and atypical antidepressants have been shown to reduce immobility in this test, although exceptions exist.[15]

Experiment 2: Olfactory bulbectomy

Adult male Sprague-Dawley rats weighing approximately 300 g at the start of the study were handled daily for a one-week acclimatization period. Bilateral olfactory bulbectomy was performed under anesthesia induced with ketamine (90 mg/kg) and xylazine (10 mg/kg), as previously described.[16] The head was shaved, and a midline sagittal incision was made extending 1 cm rostral to the bregma. Two 2-mm diameter drill holes were made in the skull, 5 mm rostral to bregma and 2 mm lateral to the midline. For sham-operated (SO) animals, the dura was pierced and the wound closed. For OB animals, the olfactory bulbs were aspirated using a water suction pump, taking care to avoid damage to the frontal cortex. The wound was sealed with a hemostatic sponge, dusted with oxytetracycline powder to prevent infection, and closed using Michel wound clips. (In previous studies using this technique, no post-surgical infections were observed.) The integrity of the surgery was confirmed at the end of the study upon euthanasia and examination of the brain. Postoperatively, animals were placed in clean bedding in their home cages and monitored closely until recovery from anesthesia (usually within ~30 min). Animals were maintained at approximately 35°C for 1 h during recovery to preserve body temperature and reduce procedure-related mortality. Animals were handled daily during a two-week recovery period prior to treatment with test substances.

Two weeks after surgery, animals were randomly assigned to treatment groups: deramciclane (5 mg/kg or 10 mg/kg), imipramine (10 mg/kg), or vehicle. Drugs were suspended in 1% hydroxyethyl cellulose and administered by intraperitoneal injection (1 ml/kg) daily between 0800 and 0900 h using 26G × ½″ (0.45 × 13 mm) needles for 14 consecutive days.

Behavioural tests following olfactory bulbectomy

Open field test

Increased locomotor activity in the open field (or ambulation score) is the most widely accepted index of olfactory bulbectomy-related behavioural changes.[17] This hyperactivity is attenuated by chronic, but not acute, administration of antidepressants and has a high predictive validity.[18] Although other measures, such as rearing (the number of times an animal simultaneously raises both forepaws off the floor), grooming (the number of self-grooming episodes), and defecation (the number of fecal boli deposited), can be assessed,[19] the ambulation score is the primary outcome measure for evaluating potential antidepressant activity. Only ambulation scores are reported in this study. The open field apparatus used was similar to that described originally and consisted of a white circular base (90 cm diameter) divided into 20 squares of 15 cm^2 by thick black lines. The surrounding wall (75 cm in height) was constructed of aluminum sheeting. Illumination was provided by a 60-W bulb positioned 90 cm above the floor of the apparatus. To prevent shadows from falling across it, the apparatus was placed on the floor of a dimly illuminated testing room. The test apparatus was carefully cleaned with a damp cloth between animals. Each rat was placed in the center of the apparatus, and the number of squares crossed (ambulation) was recorded during a three-minute testing period.

Elevated plus maze

The elevated plus maze is a validated test for anxiety, based on the natural aversion of rodents to open spaces. The apparatus used was based on the original description.[20] It consisted of a plus-shaped maze with opposing pairs of open (30 × 15 cm) and enclosed (30 × 15 × 15 cm) arms extending from a central platform (15 cm^2). The maze was elevated approximately 40 cm from the floor by supporting legs under each arm. Testing was conducted in a dimly illuminated laboratory, with indirect illumination provided by a 60-W bulb suspended 50 cm above the center of the apparatus to avoid casting shadows. An "arm entry" was defined as the point at which all four paws of the animal were fully within the boundaries of a specific arm of the maze. The cumulative time spent in, and the number of entries into, the open or closed arms were recorded during each five-minute testing session. The apparatus was thoroughly cleaned with a damp cloth between animals.

Light-dark box

The light-dark box was based on the apparatus designed for mice and adapted for rats.[21,22] The apparatus consisted of an open-top wooden box (60 × 60 cm) vertically partitioned into two equal compartments, one painted white and the other black. The light compartment was brightly illuminated by a 60-W bulb positioned approximately 80 cm above the floor. The compartments were connected by a small opening (15 × 15 cm) located centrally in the partition. The apparatus was elevated on four legs approximately 50 cm above floor level and placed in a dark testing room to prevent shadow formation. During testing, rats were placed in the center of the white compartment facing the dark compartment and observed over ten minutes. The measured outcomes included latency to enter the dark compartment, time spent in each compartment, and the number of crossings between compartments.

Physiological tests after bulbectomy

Colonic temperature was recorded by inserting a digital thermometer (RET-2 rectal probe, Physitemp Instruments Inc., Clifton, NJ, USA) 2 cm into the rectum of each rat. Temperatures were recorded at baseline, 30 and 60 min following subcutaneous injection of 8-OH-DPAT (0.15 mg/kg).

Data analysis

Data were tested for normality using the Kolmogorov–Smirnov test. For non-normally distributed data, a Kruskal–Wallis analysis of variance was performed. If the omnibus test revealed a significant effect, post-hoc comparisons were conducted using the Mann–Whitney U test. For normally distributed data, analysis of variance (ANOVA) was used, followed by the appropriate post-hoc test as indicated in the results. For the 8-OH-DPAT challenge, changes in temperature from baseline to 30 and 60 minutes post-injection were analyzed by ANOVA with post-hoc Tukey's honestly significant difference (HSD) to assess differences between treatment groups. Statistical analyses were performed using IBM SPSS Statistics (version 25).

Table 1. Effect of deramciclane on immobility time (seconds) in the forced swim test

	VEHICLE	1 MG/KG	5 MG/KG
Mean	149.4	104.1	79.4*
n	11	12	12
SEM	12.4	14.8	15.9

*$p < 0.01$ versus vehicle treated animals; n = number of animals tested. SEM, standard error of the mean.

Results

Experiment 1: Forced swim test

The effect of deramciclane on mean immobility time in the swim apparatus is presented in Table 1. A one-way ANOVA revealed a statistically significant effect of drug on immobility time ($F_{2,34}$ = 5.77; $p < 0.01$). Bonferroni post-hoc analysis indicated a significant decrease in immobility time for rats treated with deramciclane 5 mg/kg compared to vehicle-treated controls ($p < 0.01$). No significant difference in immobility time was observed for the 1 mg/kg deramciclane group relative to vehicle-treated animals.

Experiment 2: Olfactory bulbectomy

Ambulation

A one-way ANOVA showed a significant effect of group on ambulation score in the open field ($F_{7,73}$ = 5.98; $p < 0.00005$). Post-hoc Tukey's HSD tests revealed increased ambulation for OB animals compared to SO controls, except for OB animals treated with imipramine. A significant hyperactivity effect was observed in OB animals treated with vehicle compared to SO animals (difference = 38.1; 95% confidence interval [CI]: 3.5–72.7; $p < 0.05$). Chronic treatment with imipramine 10 mg/kg attenuated OB hyperactivity to levels comparable to SO animals, such that the difference was not statistically significant (difference = 11.5; 95% CI: −22.8–45.9; $p > 0.05$). In contrast, neither deramciclane 5 mg/kg (difference = 35.2; 95% CI: 2.6–67.8; $p < 0.05$) nor 10 mg/kg (difference = 39.5; 95% CI: 4.2–74.7; $p < 0.05$) significantly reduced OB hyperactivity, and activity remained elevated compared to SO animals. Data are reported in Table 2.

Elevated plus maze

Data for the elevated plus maze did not conform to a normal distribution; therefore, nonparametric analyses were performed. Kruskal–Wallis tests revealed no significant differences between groups for open arm entries (H = 5.85; df = 7; $p > 0.1$), closed arm entries (H = 7.84; df = 7; $p > 0.1$), percentage of time spent on open arms (H = 6.66; df = 7; $p > 0.1$), or percentage of time in closed arms (H = 6.98; df = 7; $p > 0.1$). Data are presented in Table 3.

Table 2. Effect of deramciclane on ambulation of olfactory bulbectomised rats in the open field test

Group	Ambulation
SO + Vehicle (n = 10)	51.1 ± 3.5
SO + Imipramine 10 mg/kg (n = 9)	56.9 ± 2.7
SO + Deramciclane 5 mg/kg (n = 10)	53.7 ± 8.0
SO + Deramciclane 10 mg/kg (n = 11)	39.8 ± 6.7
OB + Vehicle (n = 8)	89.2 ± 12.1*
OB + Imipramine 10 mg/kg (n = 9)	68.4 ± 3.0
OB + Deramciclane 5 mg/kg (n = 10)	88.9 ± 11.3*
OB + Deramciclane 10 mg/kg (n = 7)	79.3 ± 8.5*

*$p < 0.05$ versus sham operated animal with the same treatment; Data are mean ± SEM; n = number of animals tested. OB, Olfactory bulbectomized; SEM, standard error of the mean; SO, Sham operated animals.

Light-dark box

Raw data for the light-dark box test did not conform to a normal distribution and were analyzed using Kruskal–Wallis ANOVA. No significant differences were observed between groups for the number of entries into the light compartment (H = 3.71; df = 7; $p > 0.1$), the number of entries into the dark compartment (H = 5.82; df = 7; $p > 0.1$), time spent in the light compartment (H = 3.47; df = 7; $p > 0.1$), or time spent in the dark compartment (H = 2.88; df = 7; $p > 0.1$).

Hypothermic response to 8-OH-DPAT

Consistent with previous studies examining 8-OH-DPAT-induced hypothermia, no significant effect of olfactory bulbectomy surgery was observed.[23] Thus, results from SO and OB animals were combined within each treatment group, and changes from baseline in body temperature were analysed. Vehicle-treated animals exhibited a clear hypothermic response, which returned to baseline at 60 minutes post-injection. A similar pattern was observed in drug-treated groups, except for the deramciclane 10 mg/kg group, which exhibited a slight increase in temperature at 60 minutes relative to baseline (mean difference = 0.5°C). No significant differences between treatment groups were observed at 30 minutes post 8-OH-DPAT injection ($F_{3,73} = 2.28$; $p > 0.05$; ANOVA). At 60 minutes, a significant difference between groups was detected ($F_{3,73} = 2.94$; $p < 0.05$; ANOVA), which was attributable to a difference between the deramciclane 5 mg/kg and 10 mg/kg groups ($p < 0.05$; difference = 0.55°C; 95% CI: −0.04°C to 1.06°C; Tukey's HSD).

Discussion

In contrast to some previous findings, the present study demonstrated a clear antidepressant-like effect of a low dose of deramciclane in the forced swim test, a pharmacological tool with high predictive validity for identifying substances with potential clinical antidepressant activity. A distinct dose-response effect was observed, with 1 mg/kg less effective than 5 mg/kg. This finding aligns with other studies reporting activity of 5-HT2A antagonists in this test.[24,25] A previous study reported that deramciclane did not alter immobility time in the forced swim test, suggesting a lack of antidepressant-like activity.[1] Methodological differences may explain this discrepancy. The current study employed Sprague-Dawley rats, whereas the earlier study used Long-Evans rats, which exhibit lower immobility times and may impose a 'floor effect' that could mask drug activity.[26] Other factors influencing behavioural differences include age, housing conditions, and body weight, although direct comparisons are limited as these parameters were not reported in the previous study.[27] Housing conditions differed, with four rats per cage in the present study versus five in the earlier study, and overcrowding is known to affect behavioural, biochemical, and physiological outcomes in male rats.[28] Deramciclane exhibits dose-dependent effects on spontaneous locomotor activity, with an ED50 of 18 mg/kg in rats.[1] The lower doses used here (1 and 5 mg/kg) may avoid confounding effects on locomotion observed at higher doses used previously (25 and 100 mg/kg), which could artificially increase immobility. An inverted U-shaped dose-response curve may also contribute, as reported for deramciclane in the social interaction test, with efficacy observed only at lower doses.[1] Such a response may reflect the compound's mixed activity at 5-HT2A receptors (antagonist) and 5-HT2C receptors (partial agonist), consistent with other serotonergic agents demonstrating inverted U-shaped dose-response curves (e.g., yawning with lorcaserin[29]; locomotor activity with DOI[30]). Additionally, deramciclane reduced escape failures in the learned helplessness model at 1.4 and 14 mg/kg administered twice daily, and this test has relatively good predictive validity.[31]

At doses higher than those effective in the forced swim test, deramciclane did not attenuate hyperactivity induced by bilateral olfactory bulbectomy, a validated model for identifying novel antidepressants with high predictive validity.[32] The tricyclic antidepressant imipramine was active in this study, consistent with

Table 3. Effects of drug treatment on behaviour in the elevated plus maze

Group	Open arm entries	Closed arm entries	Open arm time	Closed arm time
SO + Vehicle (n = 10)	2.7 ± 0.8	6.6 ± 1.2	47 ± 21	169 ± 19
SO + Imipramine 10 mg/kg (n = 9)	2.3 ± 0.7	5.7 ± 1.2	49 ± 18	172 ± 28
SO + Deramciclane 5 mg/kg (n = 10)	1.3 ± 0.4	6.9 ± 0.9	26 ± 9	172 ± 26
SO + Deramciclane 10 mg/kg (n = 11)	2.3 ± 0.5	4.4 ± 1.2	21 ± 8	206 ± 20
OB + Vehicle (n = 8)	5.0 ± 1.6	7.0 ± 1.6	115 ± 38	116 ± 33
OB + Imipramine 10 mg/kg (n = 9)	3.0 ± 0.7	8.6 ± 1.6	85 ± 35	161 ± 31
OB + Deramciclane 5 mg/kg (n = 10)	4.1 ± 1.6	8.8 ± 1.0	45 ± 16	193 ± 19
OB + Deramciclane 10 mg/kg (n = 7)	2.7 ± 0.7	5.0 ± 1.6	56 ± 38	197 ± 36

Data are mean ± SEM; n = number of animals tested. OB, olfactory bulbectomized; SEM, standard error of the mean; SO, sham operated animals.

Table 4. Effects of drug treatment on behaviour in the light-dark box

Group	Light side entries	Dark side entries	Light side time (secs)	Dark side time (secs)
SO + Vehicle (n = 10)	2.5 ± 0.6	2.9 ± 0.7	24 ± 8	263 ± 14
SO + Imipramine 10 mg/kg (n = 9)	2.2 ± 0.7	2.5 ± 0.6	26 ± 23	265 ± 16
SO + Deramciclane 5 mg/kg (n = 10)	1.6 ± 0.2	2.4 ± 0.4	12 ± 2	282 ± 3
SO + Deramciclane 10 mg/kg (n = 11)	1.8 ± 0.3	2.7 ± 0.8	12 ± 3	273 ± 8
OB + Vehicle (n = 8)	2.9 ± 0.7	6.3 ± 1.8	13 ± 3	271 ± 8
OB + Imipramine 10 mg/kg (n = 9)	1.4 ± 0.2	2.5 ± 0.5	10 ± 4	282 ± 5
OB + Deramciclane 5 mg/kg (n = 10)	2.6 ± 1.2	3.5 ± 1.4	17 ± 4	269 ± 9
OB + Deramciclane 10 mg/kg (n = 7)	3.3 ± 1.3	4.4 ± 1.6	17 ± 9	270 ± 13

Data are mean ± SEM; n = number of animals tested. OB, olfactory bulbectomized; SEM, standard error of the mean; SO, sham operated animals.

previous reports for other compounds, including venlafaxine,[33] agomelatine,[34] mianserin,[35] and paroxetine.[36] The lack of activity of deramciclane in this model is consistent with results from the tetrabenazine-induced ptosis test, where doses above 48 mg/kg were inactive.[1] This may reflect the model's dependence on monoamine reuptake inhibition, a mechanism only weakly influenced by deramciclane.[1]

The effect of repeated administration of deramciclane on the behavior of olfactory bulbectomised and SO rats was also evaluated in two tests designed to assess anxiolytic-like activity: the elevated plus maze and the light-dark box. No statistically significant differences were observed for either the effect of surgery or treatment condition in the plus maze. This finding is consistent with previous results from this laboratory, which indicated that antidepressant drugs do not significantly alter behavior in this apparatus.[33] Nevertheless, a trend consistent with prior observations was noted, whereby OB animals exhibited hyperactivity compared to SO controls, reflected in the number of open-arm entries in vehicle-treated rats (5.0 ± 1.6 vs. 2.7 ± 0.8). Chronic treatment with imipramine reduced open-arm entries in OB animals to levels comparable to those of SO controls (3.0 ± 0.7 vs. 2.3 ± 0.7), consistent with behavior observed in the open field test. Similarly, deramciclane at 10 mg/kg reduced open-arm entries in OB animals to values similar to sham controls (2.3 ± 0.7 vs. 1.6 ± 0.5), indicating antidepressant-like behavioral effects in the bulbectomized model. No anxiolytic effect of deramciclane was observed in the elevated plus maze at doses up to 5 mg/kg.[1]

No significant effect of deramciclane on exploratory behavior in the light-dark box was detected. An earlier study similarly reported no effect at doses comparable to those used here (1 and 8 mg/kg), although deramciclane attenuated the anxiogenic effects of the 5-HT2C agonist mCPP at 3 mg/kg.[37] Increased locomotor activity of vehicle-treated OB rats was evident from the higher number of entries into the dark compartment, which was attenuated by chronic imipramine treatment (Table 4), consistent with hyperactivity observed in the open field test.

The hypothermic response to the 5-HT1A agonist 8-OH-DPAT is widely used as a measure of receptor sensitivity and is often interpreted as reflecting postsynaptic receptor activation,[38] although this remains controversial.[39] Pharmacological evidence suggests that the response may also involve dopamine D2 receptors, as it is blocked by haloperidol.[40] Chronic antidepressant treatment has generally been shown to attenuate the hypothermic response to 8-OH-DPAT in rats,[41–43] though some studies report minimal or no effect.[33] While no statistically significant differences were observed at 30 or 60 minutes, the mean data suggest that deramciclane at 10 mg/kg attenuated the response at 30 minutes (Table 5). At 60 minutes, the response differed significantly between the 5 mg/kg and 10 mg/kg doses, likely reflecting high inter-individual variability. These data may indicate involvement of 5-HT1A receptors in deramciclane's actions. However, because the hypothermic response may also involve D2 receptors, an effect at dopaminergic receptors is also possible, consistent with the known dopaminergic antagonist activity of deramciclane at high doses.[1]

Future directions

In this study, deramciclane showed contradictory evidence for antidepressant-like activity in two validated pharmacological tools that identify such potential. The compound was active in the forced swim test but inactive in the OB model. Some evidence suggested reversal of hyperactivity in OB animals in the elevated plus maze, but not in the standard open field test. In other independent tests of antidepressant-like activity, deramciclane was inactive, though the predictive validity of these models is uncertain. Further evaluation of the antidepressant-like activity of deramciclane may be warranted using animal strains and pharmacological models with higher predictive validity, alongside a detailed assessment of dose-response relationships.

Conclusions

The status of deramciclane as an antidepressant is uncertain based on the findings of the current study. Clearly further pharmacological investigations are necessary, as noted above, before expensive clinical evaluations (the definitive standard of antidepressant activity) would be undertaken.

Table 5. Hypothermic responses to 8-OH-DPAT responses

Group	Delta 30	Delta 60	N
VEHICLE	−0.49 ± 0.57	−0.01 ± 0.58	18
IMI	−0.4 ± 0.81	−0.07 ± 0.81	18
DERAM 5	−0.5 ± 0.49	−0.19 ± 0.45	20
DERAM 10	−0.045 ± 0.51	0.37 ± 0.51	18

Data represent the mean (± standard deviation) decline in rectal temperature from baseline 30 and 60 minutes after administration of 8-OH-DPAT. N = number of animals tested. OB, olfactory bulbectomized; SEM, standard error of the mean; SO, sham operated animals; 8-OH-DPAT, 8-Hydroxy-2-(di-n-propylamino)tetralin.

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Conflict of interest

Deramciclane was kindly provided by Egis Pharmaceuticals, Budapest, Hungary. The company had no role in the design of the study, data analysis, or preparation of the manuscript. Neither author reports any conflicts of interest for this study or others in the past seven years.

Author contributions

Study concept and design (TRN, CM), data acquisition (CM), data analysis and interpretation (TRN, CM), manuscript drafting (TRN), critical revision of the manuscript for important intellectual content (TRN, CM). Both authors contributed substantially to the study and approved the final manuscript.

Ethical statement

Animal care and experimental procedures were conducted in accordance with the NHMRC/CSIRO/AEC Australian Code of Practice for the Care and Use of Animals for Scientific Purposes. The study was approved by the Austin Health Animal Ethics Committee (Approval Numbers A2000/00888 and A2005/02254). Following completion of behavioral testing, all rats were euthanized according to ethical guidelines. The Forced Swim Test was conducted prior to the release of the NHMRC "Statement on the Forced Swim Test in Rodent Models" issued on 24 January 2024.

Data sharing statement

Data for this study are available from the corresponding author on request.

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