The antidepressant activity of inositol in the forced swim test involves 5-HT\(_2\) receptors

H. Einat \(^a\),*, F. Clenet \(^b\), A. Shaldubina \(^a\), R.H. Belmaker \(^a\), M. Bourin \(^b\)

\(^a\) Beer Sheva Mental Health Center, Faculty of Health Sciences, Ben Gurion University of the Negev, P.O. Box 4600, Beer Sheva, Israel
\(^b\) Department of Pharmacology, Faculty of Medicine, University of Nantes, Nantes, France

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Abstract

The effect of inositol as an antidepressant was previously demonstrated in both animal models of depression-like behavior and in clinical trials. Unlike most antidepressant drugs, inositol does not have a clear target in the synapse and was not demonstrated to alter monoamine levels in the brain. The present study attempted to draw a psychopharmacological profile of inositol's behavioral effects by exploring the interactions between the drug and specific receptor agonists and antagonists in the forced swim test. Rats received inositol treatment (or control) in combination with the serotonergic metabolism inhibitor PCPA or with the noradrenergic neurotoxin DSP-4. Results indicated that PCPA but not DSP-4 abolished the ability of inositol to cause a reduction in immobility time in the forced swim test. In mice, the specific 5-HT\(_{2A}/5-HT\(_{2C}\) antagonist ritanserin, but not the 5-HT\(_{1A}/5-HT\(_{1B}\) adrenergic antagonist pindolol, abolished inositol's effect in the forced swim test. The 5-HT\(_{2A}/5-HT\(_{2C}\) agonist DOI and the 5-HT\(_{1A}\) agonist 8-OH-DPAT did not have any significant effects on inositol's activity. The present data indicates that the antidepressant effect of inositol may involve 5-HT\(_2\) receptors. It is thus possible that the effects of reuptake antidepressant drugs and the effects of inositol may have a common final pathway. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Inositol; Depression; Serotonin receptors; 5-HT\(_2\); Forced swim test

1. Introduction

The effects of myo-inositol (henceforth referred to as inositol) treatment as an antidepressant in humans were demonstrated during the last few years [21] and chronic inositol was reported to significantly decrease Hamilton depression scale scores compared with placebo in a double blind controlled study [23]. Similar effects were also reported recently in a variety of animal models of depression where inositol administration to rats was demonstrated to reduce reserpine-induced hypoactivity, immobility time in the forced swim test [9] and to counter the innate immobility of Flinders sensitive line rats, a genetic model of depression [28] in the forced swim test [10]. Unlike other antidepressant drugs, inositol does not appear to have a direct effect in the synapse and neither acute nor chronic administration of inositol was found to change brain monoamine levels [8]. However, inositol serves as the precursor for the inositol phosphate–phosphoinositide (PIP) cycle that is the source of two second messengers, inositol 3-phosphate (IP\(_3\)) and diacylglycerol (DAG). The PIP cycle and its derived second messengers are involved in a number of neurotransmitter systems including the noradrenergic (\(\alpha-1\) receptors), serotonergic (5-HT\(_{2A}\) and 5-HT\(_{2C}\) receptors), cholinergic (muscarinic receptors) and dopaminergic (D\(_1\) and possibly D\(_2\) receptors) systems [6,36,37]. The breadth of inositol involvement in neurotransmission systems combined with its lack of direct effects in the synapse raises the question as to what are the specific mechanisms of its antidepressant activity.

Most antidepressant drugs are hypothesized to act through either the serotonergic or the noradrenergic systems or both [19]. These systems were also suggested

* Corresponding author. Tel.: +972-7-6401739; fax: +972-7-6401621.
E-mail address: haime@bgumail.bgu.ac.il (H. Einat).
to be involved in the pathogenesis of depression [1]. Since inositol is used by some receptors in both these systems, it may be possible that its therapeutic activity is also related to serotonin and/or NE, albeit not via reuptake inhibition. The Porsolt forced swim test is a behavioral model of depression [29] that is sensitive to serotonergic and noradrenergic agents [38]. This model has been used in studies to draw a psychopharmacological profile of antidepressant drugs (e.g. [31]). The basic notion of these studies is that combined administration of the studied drug with specific receptor agonists or antagonists may elucidate the mechanism of action of the drug. For example, Redrobe and his colleagues recently evaluated the effects of venlafaxine in the mice forced swim test in combination with a variety of serotonergic and noradrenergic agonists and antagonists, and were able to conclude that at low doses venlafaxine-induced behavior indicates inhibition of serotonin reuptake, whereas, at higher doses it indicates inhibition of both serotonin and noradrenaline (NE) uptake [34]. Such studies demonstrated the behavioral consequences of the multiple receptor interactions of some antidepressants and therefore suggest a number of possible mechanisms of action relevant to their therapeutic action on behavior (e.g. [4,31–35]).

The present study was designed to create a psychopharmacological profile of inositol's activity in the Porsolt model of depression. The drugs used in the present study included the serotonin metabolism inhibitor DL-p-chlorophenylalanine (PCPA), the noradrenergic neurotoxin N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP-4), the selective 5-HT₁A receptor agonist 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT), the 5-HT₁A/5-HT₁B β-adrenergic receptor antagonist pindolol, the selective 5-HT₂A/5-HT₂C receptor antagonist (+)-2,5-dimethoxy-4-iodoamphetamine (DOI) and the potent 5-HT₂A/5-HT₂C receptor antagonist ritanserin.

2. Methods

2.1. Animals

2.1.1. Rats

Male Sprague-Dawley rats (Harlan, Jerusalem), weighing 200–230 g at the beginning of experiments were housed, four to five per cage in an animal room with constant temperature (21°C) and 12 h light/dark cycle, and with free access to food and water. Rats had a 1 week acclimatization period in the animal room before the start of experiments.

2.1.2. Mice

Male Swiss mice (Centere d’elevage, Janvier, France) weighing 20–24 g at the beginning of experiment were housed, 20 per cage in an animal room with constant temperature (21°C) and 12 h light/dark cycle, and with free access to food and water.

All experiment for both rats and mice were performed during the light phase of the light/dark cycle. All rat procedures were approved by the Ben Gurion University animal experimentation ethics committee and in line with the NIH guide for the use of laboratory animals. All mice experiments were performed within the guidelines of the French Ministry of Agriculture for experiments with laboratory animals (law No. 87848).

2.2. Drugs

Inositol (SIGMA, 1 or 5 g/kg) was diluted in deionized water to an injection volume of 20 ml/kg (in rats) or 25 ml/kg (in mice). Control treatment was 1:2 glucose mannitol solution (SIGMA) at a combined dose of 5 g/kg and a dilution similar to that of inositol. Inositol treatment was administered sub-acutely as detailed in the procedure section. The doses of inositol used in the study are much higher than therapeutic doses used in clinical studies but such differences are frequent with other antidepressant drugs. For example, whereas the standard dose of imipramine for the treatment of depression is 1–4 mg/kg per day e.g. [16,20], doses used in animal experimentation range between 10 and 30 mg/kg per day e.g. [9,30].

PCPA (SIGMA) was diluted in 1% aqueous solution of Tween 80 (150 mg/100 ml) and injected intra-peritoneal (IP) at a 300 mg/kg daily dose for 3 days. Final testing in the water tank was performed 24 h after the last injection. DSP-4 (SIGMA) was diluted in deionized water (25 mg/ml) and injected IP at a 50 mg/kg dose. Final testing was performed a week after DSP-4 treatment. Pindolol (RBI, 32 mg/kg), 8-OH-DPAT (RBI, 1 mg/kg), DOI (RBI, 4 mg/kg), and ritanserin (Janssen, 4 mg/kg) were all diluted in distilled water except for pindolol that was diluted in a 1% aqueous Tween 80 solution, and injected to mice (IP) at a constant volume of 0.5 ml/20 g weight. Injections were all administrated 45 min before the exposure to the water tank.

2.3. Procedure

2.3.1. The porsolt forced swim test

2.3.1.1. Rats. The test included two exposures to a water tank (height, 40 cm; diameter, 22 cm, containing 25 cm of water at 25°C) spaced 24 h apart. The first exposure was 10 min long and the second, serving as the test session, was 5 min long. The test session was videotaped for later analysis. After each swim session, rats were placed to dry for approximately 30 min in a warmed cage before being taken back to their home cages. Analysis of videotapes was done by an experi-
enced behavioral psychopharmacologist (H.E.) who was blind to the treatment, and with a slow play mode to verify exact results.

2.3.1.2. Mice. The test included one, 6 min exposure to the water tank (height, 25 cm; diameter, 10 cm) containing 10 cm of water maintained at 23–25°C. The duration of immobility was manually recorded during the last 4 min of the session. A mouse was considered to be immobile when it floated or made only small movements necessary to keep its head above water. This method of recording was extensively used in previous studies e.g. [4,31–35] and its reliability evaluated in many studies (Bourin, unpublished observations).

2.3.2. Locomotor activity

Locomotor activity after sub-acute inositol was evaluated in rats. Animals were treated with 5 g:kg inositol (or control solution) 24 and 5 h prior to being placed in automated activity monitors. The test session continued for 30 min and data was collected for horizontal as well as vertical activity.

2.3.3. Inositol schedules

2.3.3.1. Rats. Inositol treatment (5 g/kg) consisted of two injections, the first immediately after the first exposure to the water tank and the second 5 h prior to the second exposure (the test session).

2.3.3.2. Mice. Dose response and time course experiments consisted on an acute, sub-acute or chronic treatment as detailed in the results section. For the interaction studies inositol administration included sub-acute treatment (IP), five injections at a 5 g/kg dose, administered 30, 24, 18, 12 and 6 h prior to exposure to the water tank.

2.4. Statistical analysis

Experiments designed to evaluate the effect of inositol were analyzed with either a student’s t-test or with one way analysis of variance. Time course experiment and measures for immobility time in the interaction studies were analyzed by a two way analysis of variance with inositol treatment as one factor and time or agonist/antagonist compounds as a second factor. In the time course experiments, some animals appeared to be extremely agitated after the injection (maybe due to the high volume of the injection) and therefore extreme animals that deviated more than two standard deviations from the mean were eliminated from the analysis. The number of mice eliminated was one from the 2 h group, two from the 3 h group, one from the 4 h group, two from the 5 h group and one from the 6 h group. Significance level was set at P < 0.05.

3. Results

3.1. Effects of sub-acute inositol treatment in rats

As shown in Fig. 1a inositol did not significantly influence the level of either horizontal (t-test, t(18) = 0.18, N.S.) or vertical (t-test, t(18) = 1.82, N.S.) activity. In contrast, the same schedule of treatment significantly decreased immobility time in the forced swim test (Fig. 1b; t-test, t(18) = 3.377, P < 0.004).

3.2. Inositol effects in mice: dose–response and time course in mice

Five hours after acute treatment, 5 g/kg but not 1 g/kg inositol reduced mice’s immobility time in the forced swim test compared with control animals (Fig. 2a, ANOVA, F(69) = 7.65, P < 0.001; post-hoc Scheff’ test, 5 g/kg group different than control and 1g/kg groups). As shown in Fig. 2b, the effect of 5 g/kg inositol was evident at different times after injection but most prominent at the 6 h interval (ANOVA, inositol effect — F(1) = 7.99, P < 0.01, time effect — F(5) = 1.62, N.S., interaction effect — F(5) = 1.1, N.S.; t-test for each time point, significant effect only at 6 h t(21) = 2.7, P < 0.02). Without the elimination of extreme animals (as detailed in the method section) the effects of inositol appear similar but as a non-signifi-

![Fig. 1. Activity counts (mean ± S.E.) in automated activity cages (a), filled bars — horizontal activity; stripped bars — vertical activity and Immobility time (b) in the forced swim test for rats treated with sub-acute 5 g/kg inositol or control solution. n = 10 per group, significance level set at P < 0.05.](image-url)
3.3. Inositol–PCPA interaction in rats

The administration of PCPA to rats resulted in a decrease in immobility time tested in the Porsolt forced swim test, but abolished the effect of inositol to decrease immobility (Fig. 3; ANOVA — PCPA effect, \( F(1) = 54.5, \) \( P < 0.0001 \); Inositol effect, \( F(1) = 0.8, \) N.S.; PCPA by Inositol interaction, \( F(1) = 7.13, \) \( P = \) 0.01), post-hoc (LSD), control-control different than control-inositol, but not different than PCPA-inositol.

3.4. Inositol–DSP-4 interaction in rats

As shown in Fig. 4, the damage to NE neurotransmission by the neurotoxin DSP-4 did not have an effect on immobility time in the forced swim test, nor on the effect of inositol in this model (ANOVA — DSP-4 effect, \( F(1) = 0.8, \) N.S.; Inositol effect, \( F(1) = 6.64, P < 0.02; \) DSP-4 by Inositol interaction, \( F(1) = 2.1, \) N.S.).

3.5. Interactions of inositol with specific antagonists and agonists in mice

Sub-acute treatment with inositol reduced immobility time in the forced swim test for mice. As shown in Table 1, the reduction was not significantly affected by the administration of a number of specific receptor agonists and antagonists (\( n = 10 \) per group, ANOVA — Inositol effect, \( F(1) = 9.58, \) \( P < 0.003; \) agonists/antagonists effect, \( F(4) = 1.28, \) N.S.; Interaction effect, \( F(4) = 1.51, \) N.S.). No other apparent effects (such as DOI-induced head twitches) were observed. However, a strong trend was observed for the effect of inositol to reduce immobility time to be blocked by the 5-HT2A/5-HT2C antagonist ritanserin. We, therefore, tested ritanserin individually.

3.6. Interaction of inositol with ritanserin

Sub-acute inositol injections (5 g/kg, 42, 30, 18 and 6 h before testing) significantly decreased immobility time in the forced swim test in mice. The effect was abolished by a single ritanserin injection (4 mg/kg) administered 45 min before testing (Fig. 5; ANOVA, inositol effect — \( F(1) = 0.8, \) N.S.; ritanserin effect — \( F(1) = 1.5, \) N.S.; inositol by ritanserin interaction — \( F(1) = 12.6, P < 0.001; \) post-hoc Scheff’ test, inositol-control different than placebo-control and different than inositol-ritanserin).
The present study replicates previous reports [9] of antidepressant effect of inositol in the forced swim test. Furthermore, it shows that these effects are consistent across species (rats and mice) and across laboratories. Inositol administration resulted in reduced immobility time in the forced swim test in rats. This effect was not observed after treatment with the serotonin metabolism inhibitor PCPA but was not influenced by the treatment with the noradrenergic neurotoxin DSP-4. These findings suggest that inositol effects may be related to the serotonergic but not the noradrenergic system. Selective effects on 5-HT1A or 5-HT1B receptors, either with an agonist (8-OH-DPAT) or with an antagonist (pindolol) did not influence the anti-immobility effect of inositol in the model. However, the administration of the 5-HT2A/5-HT2C antagonist ritanserin abolished inositol’s effects.

Inositol was recently demonstrated to increase locomotor activity [17]. This effect appears to lessen the strength of possible conclusions regarding antidepressive-like effects in the forced swim test. However, the reported effects of inositol as an anti-anxiety agent both in humans [21] and in animals [7] suggests that the increased activity observed during a first exposure to novel environment [18] may be related to inositol’s anxiolytic properties rather than to direct hyperactivity effect. Furthermore, inositol did not increase levels of ambulation in the reserpine-hypoactivity model [9] and, in the forced swim test, it was observed to increase not only total activity time, but also struggle time, a measure that may reflect not just general hyperactivity but possibly a reduction in levels of despair [9]. Thus, it appears that the action of inositol in the model is of a specific antidepressant-like nature and not as a general psychostimulant.

PCPA itself reduced immobility time in the present study and this effect was replicated in another experiment (data not shown). This effect of PCPA may be related to its reported effects on activity levels in general e.g. [14,15] and not related to a specific antidepressant effect. PCPA acts pre-synaptically and its interaction with inositol may indicate that inositol’s action may be dependent on pre-synaptic mechanisms; e.g. adequate serotonin release may be necessary for inositol to enhance post-synaptically the intracellular effects of 5-HT2 receptor stimulation. The robust effect of PCPA itself to reduce immobility makes the findings regarding inositol hard to interpret. Beyond the hypothesized possibility that the abolishment of inositol’s effect is related to the inhibition, by PCPA, of serotonergic pathways, it is also possible that the reason that the anti-immobility effect of inositol was not observed when co-administered with PCPA is a ceiling effect induced by PCPA. It is also possible that inositol may have similar effects to PCPA in this model and therefore no further decrease in immobility should occur. Yet, the possibility that inositol’s effects are related to the serotonergic system is supported by the experiment with ritanserin.

The effects of some selective serotonin reuptake inhibitors (SSRI’s) in the forced swim test were previously demonstrated to be mediated through 5-HT1A autoreceptors as well as 5-HT1B postsynaptic receptors [33]. However, the same authors suggest that SSRI’s may also act partially through 5-HT3 receptors and that tricyclic antidepressants may be acting through 5-HT2A/5-HT2C receptor sites [31]. The present data indicate that inositol’s spectrum of receptor interactions in the forced swim test may be similar to that of other antidepressants with regard to 5-HT mechanisms but may be partially different from both SSRIs and tricyclics regarding the specific receptors involved. Considering the heterogeneity of receptors linked to the PI cycle it is

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**Table 1**

<table>
<thead>
<tr>
<th>Agonist/antagonist pretreatment</th>
<th>Vehicle</th>
<th>8-OH-DPAT</th>
<th>Pindolol</th>
<th>DOI</th>
<th>Ritanserin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>220.4 ± 2.9</td>
<td>224.1 ± 4.1</td>
<td>227.6 ± 2.9</td>
<td>216.5 ± 3.2</td>
<td>218.2 ± 5.0</td>
</tr>
<tr>
<td>Inositol</td>
<td>207.3 ± 6.8</td>
<td>215.9 ± 4.5</td>
<td>209.9 ± 4.4</td>
<td>208.1 ± 3.9</td>
<td>221.5 ± 5.9</td>
</tr>
</tbody>
</table>

* Inositol significantly reduced immobility time without a significant interaction (n = 10 per group, ANOVA — inositol effect, F(1) = 9.58, P < 0.003; agonists/antagonists effect, F(4) = 1.28, N.S.; interaction effect, F(4) = 1.51, N.S.). A trend was observed for inositol effect to be blocked by the 5-HT2A/5-HT2C antagonist ritanserin.

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4. Discussion

The present study replicates previous reports [9] of antidepressant effect of inositol in the forced swim test. Furthermore, it shows that these effects are consistent across species (rats and mice) and across laboratories. Inositol administration resulted in reduced immobility time in the forced swim test in rats. This effect was not observed after treatment with the serotonin metabolism inhibitor PCPA but was not influenced by the treatment with the noradrenergic neurotoxin DSP-4. These findings suggest that inositol effects may be related to the serotonergic but not the noradrenergic system. Selective effects on 5-HT1A or 5-HT1B receptors, either with an agonist (8-OH-DPAT) or with an antagonist (pindolol) did not influence the anti-immobility effect of inositol in the model. However, the administration of the 5-HT2A/5-HT2C antagonist ritanserin abolished inositol’s effects.

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**Fig. 5** Immobility time (mean ± S.E.) in the forced swim test for mice treated with sub-acute inositol and with ritanserin (in a 2 x 2 design), n = 16 per group, significance level was set at P < 0.05.
reasonable that its action is similar to the broad acting tricyclics rather than to the more specific SSRIs.

The present findings are consistent with reports that 5-HT₂ but not 5-HT₁ receptors are linked to the PI cycle [6]. These findings may offer a rationale for clinical findings indicating therapeutic effects of inositol in the same range of psychiatric disorders affected by SSRIs i.e. depression [23], panic [3], obsessive compulsive disorder [11] and bulimia [13] and a lack of effect in other psychiatric disorders such as schizophrenia [22], autism [25], Alzheimer’s disease [2] and attention deficit disorder [24].

If inositol effects are indeed related to 5-HT₂A/₂C receptors it could have been expected that its action would be potentiated by DOI. Such potentiation was not observed in the present study. This lack of potentiation may be a result of a ceiling effect and is similar to clinical findings that found no augmentation with a combination treatment of inositol and SSRIs in depressed patients [26]. It is also a possibility that inositol effects could be related to non-serotonergic systems. For example, 5-HT₂ receptors were shown to control HPA axis activation e.g. [5] and be involved in the modulation of dopamine outflow in the striatum e.g. [27]. It is conceivable that inositol effects are mediated through either of these systems and the modification of effects achieved here with serotonergic agents is the result of an interaction between serotonergic receptors and non-serotonergic systems.

We found no effects on monoamine levels of acute or chronic inositol treatment [8]. This contrasts with the reuptake antidepressant drugs that acutely modulate monoamine levels. However, it is now accepted that the acute effects of classical antidepressants in the synapse is not the primary source of their therapeutic activity and considerable research is now directed at testing possible changes caused by the antidepressant drugs in ‘downstream’ aspects of neurotransmission such as modulation of receptors or of second messengers systems (for review see [19]). The understanding of the mode of therapeutic activity of drugs can also provide insight into the possible etiology of depression itself.

The reports indicating that inositol, an important substrate for second messenger synthesis, is effective in the treatment of depression [21] and the reversal of depressive-like behaviors in animals [7,9,10] provide support to the possibility that the mechanisms of action of antidepressant drugs are related to alterations in second messengers systems. The results of the present study that demonstrate a link between the effect of inositol in a depression-like animal model and specific serotonergic receptors may suggest that the final pathway responsible for the antidepressant effects of inositol and of other antidepressants may be similar. However, inositol and the PI cycle are linked to other neurotransmitter systems other than the serotonergic and noradrenergic systems evaluated in the present study. It is therefore possible that these systems may also be involved in inositol’s mode of action as an antidepressant and further studies are needed to evaluate this option.

Two recent clinical studies [12,26] found that inositol treatment gave no added benefit to patients treated with adequate doses of SSRIs for depression [26] or obsessive compulsive disorder [12]. If inositol and SSRIs share a final common pathway, this could explain therapeutic efficacy for both compared with placebo but no additive benefit of the drug combination.

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