Antidepressants specifically inhibiting noradrenaline reuptake enhance recognition memory in rats

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Summary

Antidepressants that specifically inhibit noradrenaline reuptake enhance memory in a version of the novel object recognition test, in which rats naturally forget the objects after 24hrs. The finding that serotonin reuptake inhibitors (SSRIs) and the cyclic antidepressants mianserin and desipramine improve recognition memory if injected after, but not prior to, the training phase indicates that these antidepressants might inhibit memory acquisition. Our data therefore support the notion that noradrenaline reuptake inhibitors (NRIs) appear to be more effective than SSRIs on cognitive deficits in depression.

Background

Cognitive deficits in depression often remain even after remission of affective symptoms and impair functional recovery, indicating that the overall treatment of depression is insufficient. However, the effects of antidepressants on cognition have hardly been studied. Harmer and co-workers (2009) have shown that even a single dose of the antidepressant reboxetine modifies the negative affective bias in face recognition and word memory in depressed patients. These findings led to the theory that antidepressants rapidly improve emotional processing leading to a more positive view of the world, which over time may improve mood. In this study, we tested reboxetine, in comparison to other antidepressants, for its effect on episodic memory by using the novel object recognition test in rats and investigated the role of dopamine in reboxetine's effect on recognition memory.

Results

Acute administration of antidepressants selectively inhibiting noradrenaline reuptake improves recognition memory

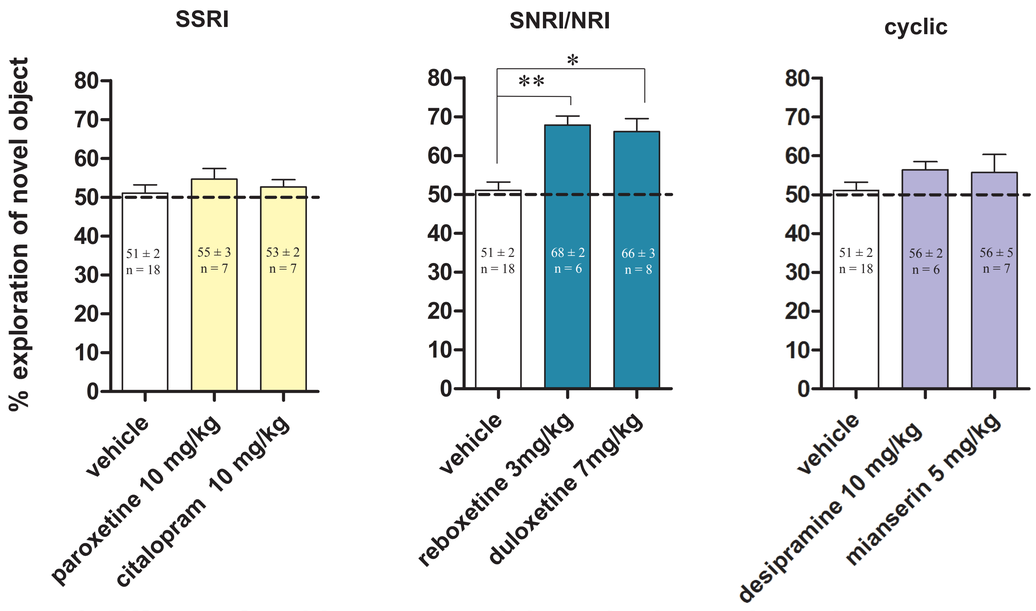

Figure 2. Effects of antidepressants injected prior to the training phase on recognition memory

30 min prior to the training phase male Sprague-Dawley rats were injected with an acute dose of an antidepressant and tested for recognition memory 24 hrs later. Data is presented as mean % exploration of the novel object ± SEM. *=p<0.05, **=p<0.01 compared to vehicle.

Reboxetine's effect on recognition memory is dopamine-dependent and cannot be inhibited by pre-treatment with an SSRI

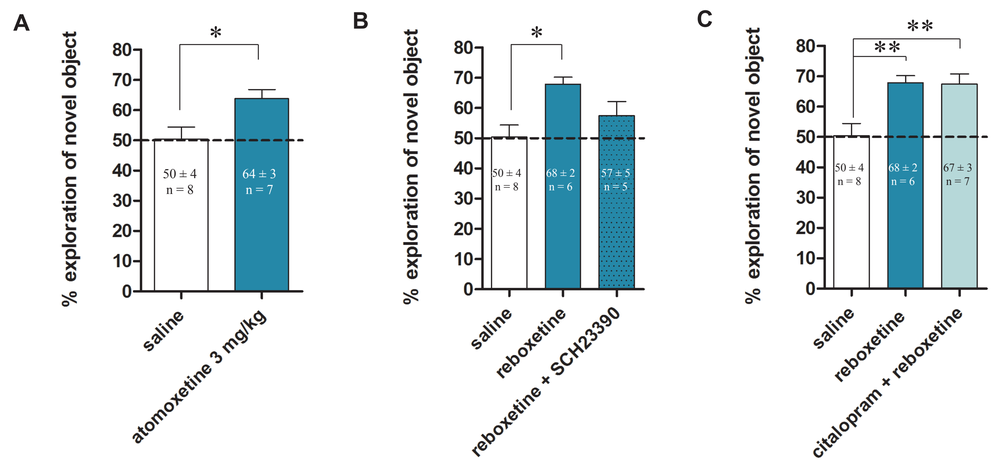

Figure 4. Effects of another NRI and treatment combinations on recognition memory

A) To confirm that noradrenaline reuptake inhibition improves novel object recognition, atomoxetine was injected 30 min prior to the training phase. **B)** Injection of the D1 antagonist SCH23390 (0.1 mg/kg) directy after the training phase abolished the memory-enhancing effect of 3 mg/kg reboxetine injected 30 min prior to the training phase. **C)** Injection of the SSRI citalopram (10 mg/kg) 35 min before the training phase could not abolish reboxetine's memory-enhancing effect **A-C)** Data is presented as mean % exploration of the novel object ± SEM. *=p<0.05, **=p<0.01 compared to saline.

Methods

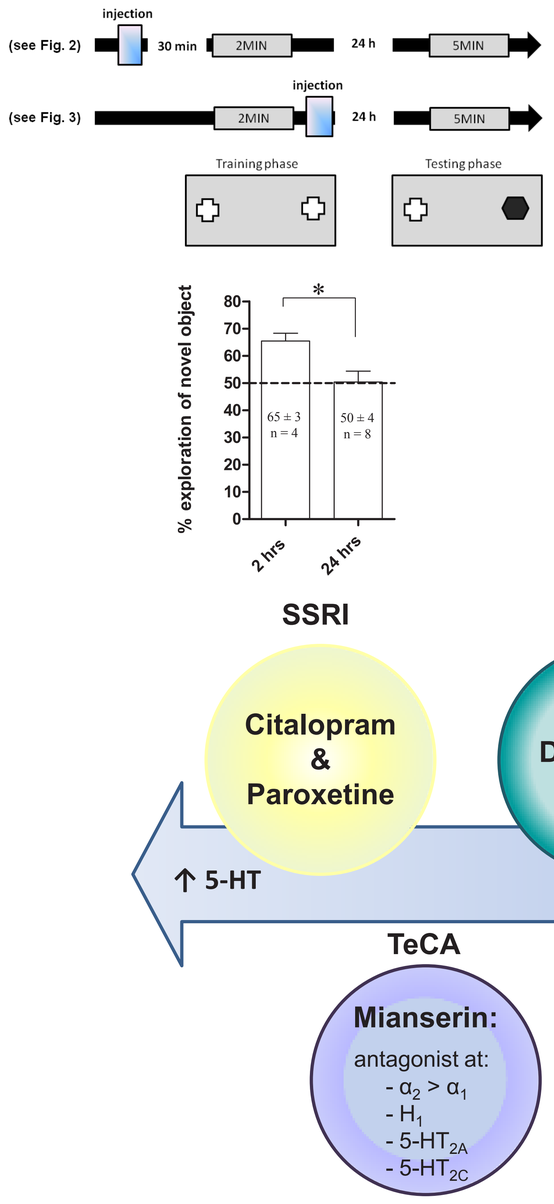

Figure 1. A behavioral model for testing drugs for memory-enhancing effects

In the training phase of the novel object recognition test (Ennaceur and Delacour 1988) rats are presented to two identical objects for 2 min. After a delay, rats are allowed to explore a novel and a familiar object. After a 2h-delay, rats show a preference for the novel object indicating that they remember the familiar object. However, after a 24h-delay this preference is not present. Data is presented as exploration of the novel object as percentage of the total exploration time and analyzed by one-way ANOVA followed by Newman-Keul's post hoc test or student's t-test (Fig. 1, 4A).

Acute administration of antidepressants after the training phase improves recognition memory

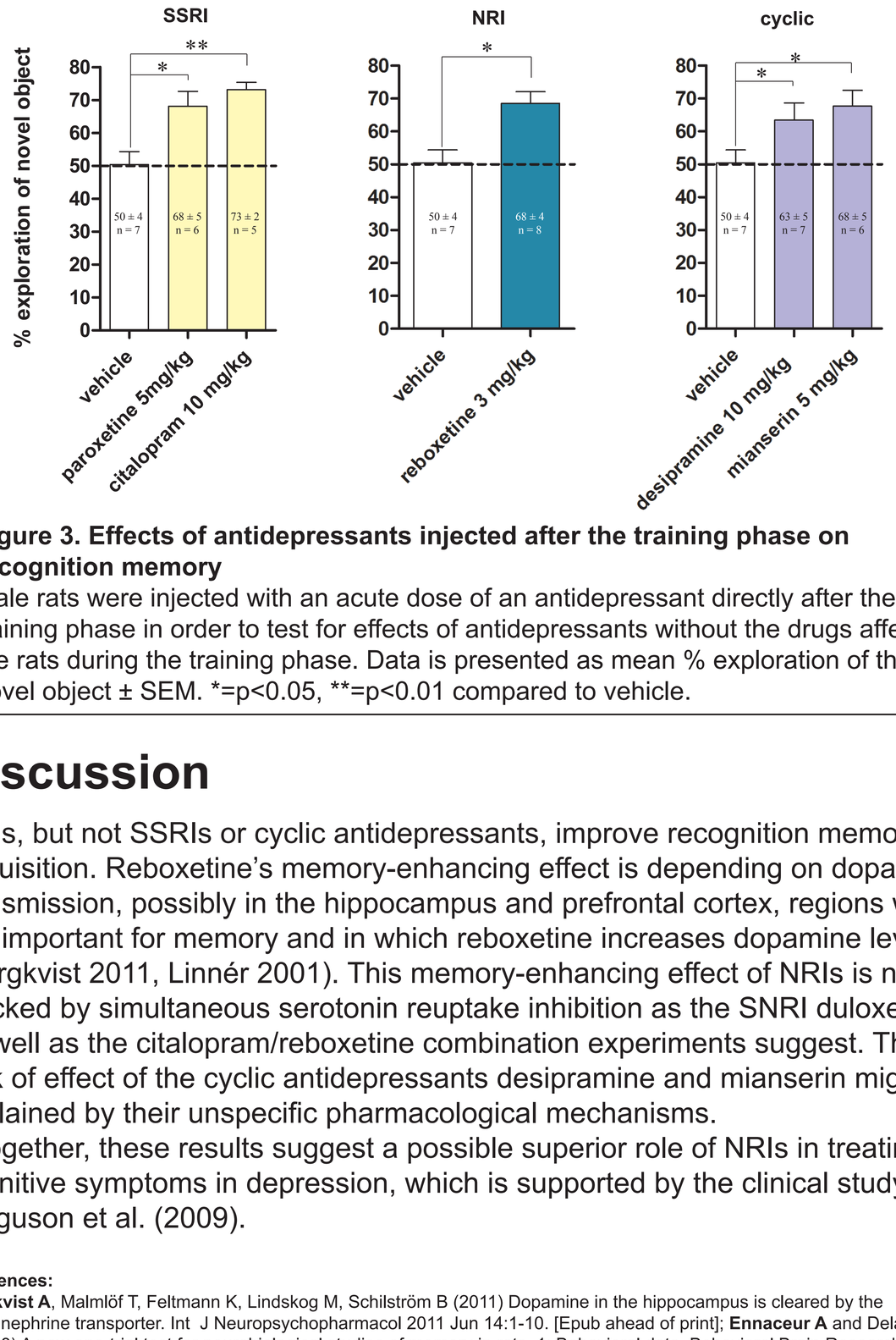

Figure 3. Effects of antidepressants injected after the training phase on recognition memory

Male rats were injected with an acute dose of an antidepressant directly after the training phase in order to test for effects of antidepressants without the drugs affecting the rats during the training phase. Data is presented as mean % exploration of the novel object ± SEM. *=p<0.05, **=p<0.01 compared to vehicle.

Discussion

NRIs, but not SSRIs or cyclic antidepressants, improve recognition memory acquisition. Reboxetine's memory-enhancing effect is depending on dopamine transmission, possibly in the hippocampus and prefrontal cortex, regions which are important for memory and in which reboxetine increases dopamine levels (Borgkvist 2011, Linnér 2001). This memory-enhancing effect of NRIs is not blocked by simultaneous serotonin reuptake inhibition as the SNRI duloxetine as well as the citalopram/reboxetine combination experiments suggest. The lack of effect of the cyclic antidepressants desipramine and mianserin might be explained by their unspecific pharmacological mechanisms.
Altogether, these results suggest a possible superior role of NRIs in treating cognitive symptoms in depression, which is supported by the clinical study of Ferguson et al. (2009).

References:
Borgkvist A, Malmlöf T, Feltmann K, Lindskog M, Schilström B (2011) Dopamine in the hippocampus is cleared by the norepinephrine transporter. Int J Neuropsychopharmacol 2011 Jun 14:1-10. [Epub ahead of print]; **Ennaceur A** and Delacour J (1988) A new one-trial test for neurobiological studies of memory in rats. 1: Behavioral data. Behavioral Brain Research 31:47-59.; **Ferguson** JM, Wesnes KA and Schwartz GE (2003) Reboxetine versus paroxetine versus placebo: effects on cognitive functioning in depressed patients. Int Clin Psychopharmacol 18:9-14. **Harmer CJ**, O'Sullivan U, Favaron E, Massey-Chase R, Ayres R, Reinecke A, Goodwin GM and Cowen PJ (2009) Effect of acute antidepressants administration on negative affective bias in depressed patients. Am. J. Psychiatry 166:1178-1184.; **Linnér L**, Endersz H, Ohman D, Bengtsson F, Schalling M. and Svensson TH (2001) Reboxetine modulates the firing pattern of dopamine cells in the ventral tegmental area and selectively increases dopamine availability in the prefrontal cortex. J Pharmacol Exp Ther 297:540-546.

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