Antidepressants specifically inhibiting noradrenaline reuptake enhance recognition memory in rats

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Summary
Antidepressants that specifically inhibit noradrenaline reuptake enhance recognition 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.

Methods

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 noradrenaline reuptake inhibitors 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) directly 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.

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 (Borgvist 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 mechanism.

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: