THE α7 nACh RECEPTOR AGONIST, SSR180711, DISPLAYS ANTIDEPRESSANT-LIKE EFFECTS IN RODENTS

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Psycho Pharmacology

Introduction

■ Both depression and Alzheimer's disease are prevalent disorders in old age and may co-occur in the same individual. Moreover, fifty percent of schizophrenic patients suffer from comorbid depression, which is a major risk factor for suicide in this population. Both human and animal studies suggest a strong involvement of the α7 nicotinic receptor (α7 nACh) in the physiopathology of Alzheimer's disease and schizophrenia. Earlier pharmacological experiments in rodents have demonstrated that the stimulation of the α7 nACh receptor with the selective partial agonist SSR180711 (Biton et al., 2004; Vigé et al. 2004), may improve cognitive functions in a variety of animal models (Bergis et al., 2004; Pichat et al., 2004). To evaluate whether the stimulation of α7 nACh receptors may also yield antidepressant-like effects, the activity of SSR180711 was evaluated in different models of depression, including the forced-swimming test in rats, the separation-induced distress calls test in rat pups and the "chronic mild stress" procedure (CMS) in mice. These models are known to be sensitive to the action of the prototypical SSRI antidepressant fluoxetine.

Chemical structure of SSR180711
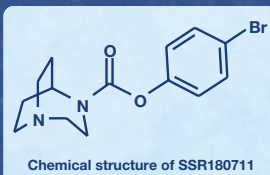
Methods

Forced-swimming test in rats

■ The procedure was a modification of that described by Porsolt et al. (1977). Wistar rats (200-250 g) were placed in individual glass cylinder (40 cm height, 17 cm diameter) containing water (21°C) to a height of 30 cm. Two swimming sessions were conducted (an initial 15-min pretest followed 24 h later by a 6-min test). The duration of immobility was measured during the 6-min test. Drugs were given p.o. twice (15 min after the first session on day 1 and 60 min before the test on day 2).

Separation-induced ultrasonic distress calls in rat pups

■ The procedure used was adapted from the technique described by Gardner (1985). Each 7-day old pup (OFA rats) was first separated from its mother and littermates for subcutaneous injection of the compound and returned to its mother. Thirty minutes later, the pup was placed in a soundproof cage (30x30x15 cm). The Ultravox system (Noldus, Wageningen, The Netherlands) was used to record ultrasonic vocalizations (40 kHz). A modified ultrasound detector (Mini-3 bat model) connected to a microphon (positioned next to the pup) was used to transform ultrasonic sound into audible sound. The signal was then filtered and sent to a computer for analysis. Each bout of distress call that lasted more than 10 ms was recorded during 3 minutes.

Chronic mild stress (CMS) procedure in mice

■ The CMS in mice (Griebel et al., 2002) consisted in the sequential application of a variety of mild stressors to individually housed male BALB/c mice (6-week old), including restraint, forced swimming, access to an empty bottle, pairing with another stressed animal, wet sawdust, during 36 days. Daily administrations of SSR180711 (10 mg/kg, i.p.) started on day 15 and lasted 22 days. Effects of fluoxetine (10 mg/kg, i.p.) were evaluated in the same experiment. Parallels between depression in humans and the behavior of chronically stressed animals have been drawn on the difficulty of the patient to accomplish even the smallest tasks (e.g. washing and dressing in the morning) leading to the inability to maintain minimal personal hygiene, and the decrease in grooming behavior seen in chronically stressed animals. In this latter case, there is a degradation of the physical state of the coat, consisting mainly in dirty and/or loss of fur. Based on these observations, we measured physical state of the coat once a week over the entire CMS period, using the following scale:

▶ **3 points:** clean and well groomed coat
▶ **2 points:** disorganized (poorly groomed) coat on the back
▶ **1 point:** dirty coat with loss of patches of fur

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
am	Sawdust change / Restraint (1h)	Weight and physical state measures / Restraint (1h)	Forced swim in water 35°C (30')	Empty bottle (2h)	Restraint (1h)	Scramble LD cycle	Scramble LD cycle
pm	Restraint (1h)	Pairing on wet sawdust (10')	Restraint (1h) / Water and food deprivation (overnight)	Forced swim in water 35°C (30')	Darkness (2h) / Wet sawdust (72h)	Scramble LD cycle	Scramble LD cycle

EXAMPLE OF A ONE-WEEK STRESS SCHEDULE

Results

Figure 1 — SSR180711 REDUCED IMMOBILITY TIME IN THE FORCED-SWIMMING TEST IN RATS

Each bar represents the mean (+ SEM) duration of immobility during a period of 6 min. *P<0.05 versus vehicle, Dunnett test.

Figure 2 — SSR180711 DECREASED SEPARATION-INDUCED DISTRESS CALLS IN RAT PUPS
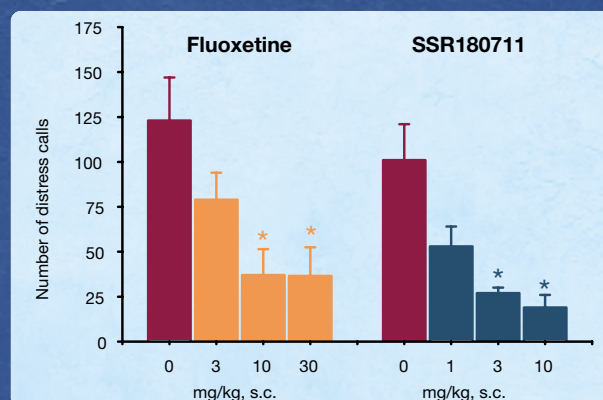
Each bar represents the mean (+ SEM) frequency of ultrasonic calls emitted during a 3-min separation period. *P<0.05 versus vehicle, Dunn test.

Figure 3 — SSR180711 REVERSED THE PHYSICAL DEGRADATION INDUCED BY CHRONIC UNPREDICTABLE STRESS IN MICE
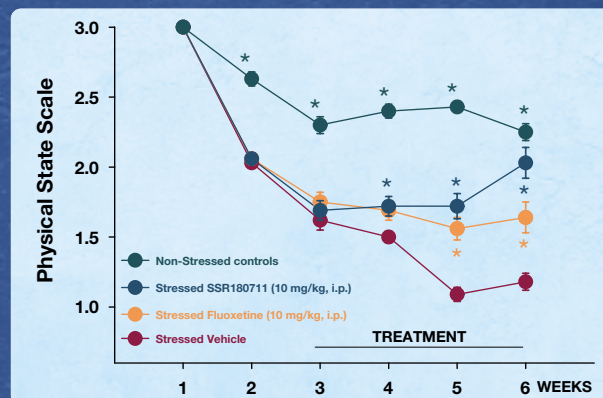
Each symbol represents the average (+ SEM) physical state score recorded every week of the 6-week application of chronic mild stress in SSR180711 - and fluoxetine - treated mice. *P<0.05 compared to stressed controls, Wilcoxon or Dunn test.

Conclusion

■ SSR180711 showed clear efficacy in different well-validated animal models predictive of an antidepressant-like activity such as the forced-swimming test in rats, the ultrasonic distress calls test in rat pups and the chronic mild stress procedure in mice.

■ The antidepressant-like effects were comparable to those observed with the prototypical antidepressant fluoxetine.

■ These results suggest that SSR180711 is endowed with antidepressant-like properties indicating that α7 nACh receptor agonists may reduce symptoms of depression associated with Alzheimer's disease or schizophrenia.
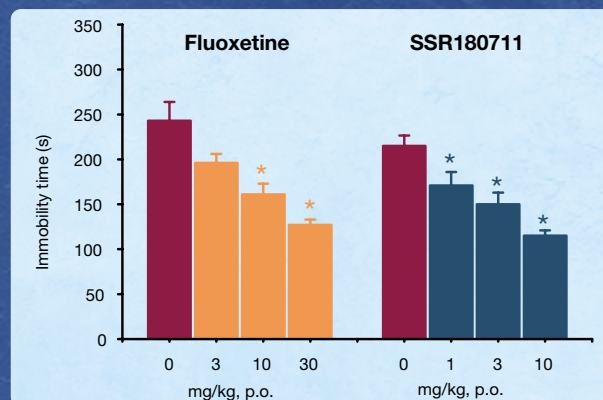
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