EFFECTS OF THREE NEUROKININ ANTAGONISTS AT THE NK1, NK2, OR NK3 RECEPTOR - SSR240600, SAREDUTANT, OSANETANT - ON THE DRL-72s SCHEDULE IN RATS

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Introduction

- Tachykinins have been shown to play a role in a variety of psychiatric diseases, including depression, anxiety disorders and schizophrenia. SSR240600, saredutant (SR48968) and osanetant (SR142801) are antagonists at the neurokinin NK1, NK2 or NK3 receptor, respectively. Here, we sought to assess the antidepressant-like potential of these compounds in rats submitted to the differential reinforcement of low rate (DRL)-72s paradigm, an operant procedure validated for its sensitivity to antidepressants [1,2]. The prototypical antidepressant, fluoxetine, was used as a positive control.

Material and Methods

Animals

- Male Wistar rats were purchased from Iffa Credo (France). They were maintained singly under a 12:12 LD cycle (lights on at 07:00 a.m.) with *ad libitum* access to water but a restricted access to food (20 g of food chow per day).

The DRL-72s schedule

- Rats were trained to press a lever to obtain a food pellet (FI 60s – CRF_1) in a skinner box. After acquiring lever pressing for food pellets, rats were successively trained in a DRL-15s, followed by a DRL-30s and then finally a DRL-72s. Explicitly, the DRL-72s schedule requires rat to wait at least 72 s between 2 lever presses to earn a food pellet. A response emitted before 72s elapsed, resets the timer to 0s.

Drug administration

- SSR240600, saredutant (SR48968), osanetant (SR142801) and fluoxetine were suspended in saline with a drop of Tween 80. The drugs were administered intraperitoneally (1 ml/kg of body weight), 30 min before starting operant schedule.

Statistical analysis

- The total number of lever presses, the percentage of reinforced lever presses (vs. total number of lever presses), the percentage of responses emitted in bin [48-96s] after obtaining a reinforcement, were analyzed with a Friedman's test, followed by a multiple comparison test, taking the control performance [mean of three sessions under vehicle treatment] as the reference group. The distribution of the responses (Inter Response Time - IRT) was statistically analyzed with a Cochran-Mantel-Haenszel test applied to nine classes of intervals.

Conclusion

- **In comparison to fluoxetine, SSR240600 and saredutant displayed a behavioural profile similar to fluoxetine in the DRL-72s schedule, confirming that NK1 and NK2 antagonists may represent an interesting therapeutic approach for the treatment of depression.**

Results

- As expected for an antidepressant tested in the DRL-72s paradigm, fluoxetine (5-10 mg/kg, i.p.) decreased the total number of responses, increased reinforced response frequency [Table 1] and shifted the IRT distribution of responses toward longer IRT durations without disrupting the profile of the IRT distribution, from the dose of 2.5 mg/kg [Figure A]. These effects are classically reported with antidepressant drugs [1,2].

  SSR240600 (3-10 mg/kg, i.p.) and saredutant (3-10 mg/kg i.p.) increased reinforced response frequency, decreased the total number of responses [Table 1] and shifted the IRT frequency distribution toward longer IRT durations without changing the shape of the IRT distribution [Figures B and C]. Osanetant (10-30 mg/kg, i.p.) did not alter the total number of responses and the reinforced responses frequency [Table 1, Figure D].

EFFECTS OF FLUOXETINE, SSR240600, SAREDUTANT AND OSANETANT ON IRT DISTRIBUTION OF LEVER PRESSES IN A DRL-72 S SCHEDULE IN RAT.

Figure A FLUOXETINE

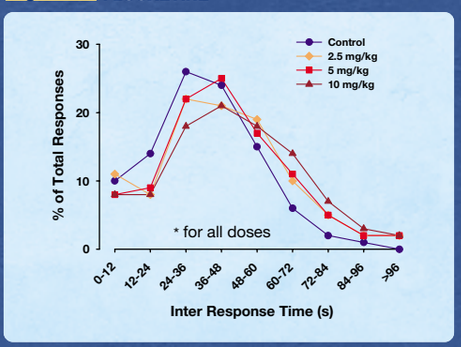


Figure B SSR240600 (NK1 ANTAGONIST)

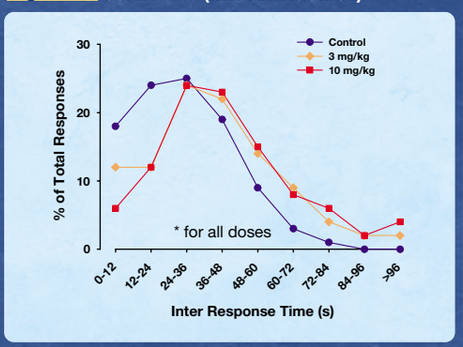


Figure C SAREDUTANT (NK2 ANTAGONIST)

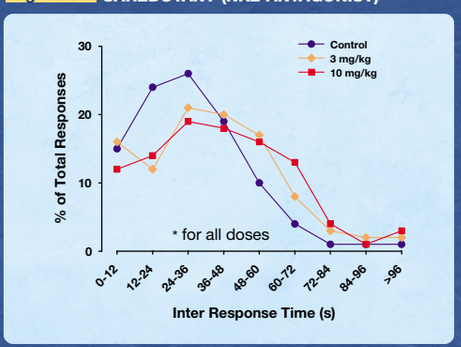
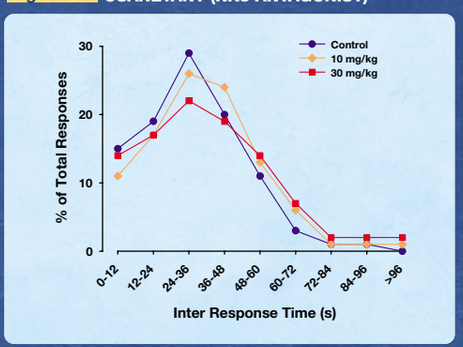


Figure D OSANETANT (NK3 ANTAGONIST)



Drugs were injected i.p., 30 min before starting experiment. Data are expressed as the average percentage of lever-presses emitted during each IRT bin (with respect to the total number of lever-presses). Error bars are omitted for clarity. Drug or vehicle was injected i.p., 30 min pre-session.
* $p < 0.05$ post-hoc test (Bonferroni-Holm's correction factor) vs. vehicle-treated group, following a significant Cochran-Mantel-Haenszel analysis applied to 9 classes of IRT. N=8 rats per group.

Table 1 EFFECTS OF FLUOXETINE, SSR240600, SAREDUTANT AND OSANETANT ON THE PERCENTAGE OF REINFORCED LEVER PRESSES, ON THE PERCENTAGE OF LEVER PRESSES PERFORMED IN THE BIN (48-96 S) AND ON THE TOTAL NUMBER OF LEVER PRESSES.

Drugs	Doses (mg/kg)	% of reinforced lever presses	% of responses in IRT 48-96 s	Total number of lever presses
• **Fluoxetine** *(n=8)*	C	3 ± 1	24 ± 5	100 ± 4
	2.5	9 ± 1	36 ± 6	87 ± 4
	5	9 ± 1	35 ± 4	85 ± 3 *
	10	13 ± 2 **	42 ± 5 *	79 ± 5 **
• **SSR240600** *(n=8)*	C	2 ± 1	13 ± 1	124 ± 4
	3	7 ± 2	29 ± 4 *	96 ± 9 *
	10	12 ± 3 **	30 ± 4 *	84 ± 5 *
• **Saredutant** *(n=8)*	C	3 ± 1	16 ± 2	117 ± 5
	3	6 ± 2 *	30 ± 4 *	98 ± 6 *
	10	9 ± 2 *	35 ± 4 **	88 ± 5 **
• **Osanetant** *(n=8)*	C	2 ± 1	16 ± 3	118 ± 6
	10	3 ± 1	21 ± 3	103 ± 3
	30	7 ± 3	26 ± 5	103 ± 9

* $p < 0.05$, ** $p < 0.01$ *vs.* control performances (C) : Friedman analysis followed by multiple comparison test

References

1. Seiden LS., Dahms JL., Shaughnessy RA. *Psychopharmacology* (1985) 86: 55-60.
2. Mc Guire PS., Seiden LS. Pharmacol. Biochem. Behav. (1980) 13: 691-694.

Acknowledgements

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