THE β_3 ADRENOCEPTOR AGONIST, SR58611A, DISPLAYS ANXIOLYTIC-LIKE EFFECTS IN RODENTS

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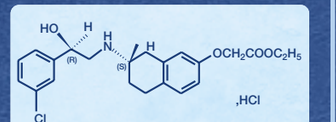
Introduction

- β adrenoceptors of the β_1 and β_2 subtypes are known to play a role in depression and anxiety-related disorders. However, little is known about the implication of β_3 adrenoceptors in stress-related disorders. Earlier experiments in rodents have demonstrated that the stimulation of the β_3 receptor subtype with SR58611A resulted in antidepressant-like effects (Simiand et al., 1992, Stemmelin et al., 2004). It was hypothesized that the compound may also have stress-attenuating properties. Thus, the present study aimed at investigating the effects of SR58611A in classical models of anxiety using different species and models based on ethological-oriented techniques that reflect different emotional states. Moreover, SR58611A was also tested for potential side effects classically observed with benzodiazepines.



Chemical structure of SR58611A

Methods

- Effects of SR58611A were assessed in a variety of classical animal models of anxiety, including 4-plate test in gerbils, Vogel punished drinking and elevated plus-maze tests in rats. Social interactions in gerbils and mice and the consequence of a mouse social defeat stress were also evaluated. The mouse defense test battery, a sensitive and appropriate tool for preclinical evaluation of anxiety-modulating drug, was used to test the effects of SR58611A on defensive reactions. The present study also investigated if SR58611A produced the adverse side effects classically observed with benzodiazepines: muscle relaxant effects and pharmacodynamic interaction with alcohol (using the rotarod test in mice), sedative properties (different measures of locomotion in mice and rats), amnesic effects (short term episodic memory in the object recognition task in mice, spatial reference memory in the Morris water maze in rats), and increase in anxiety produced by withdrawal from a 10-day repeated treatment. These tests have been described in details in Griebel et al., 2001, 2002.

Drugs

- The drugs used were SR58611A and diazepam. Compounds were prepared as solutions (SR58611A) or suspensions in physiological saline or distilled water containing 0.5% Tween80. Drugs administered intraperitoneally (i.p.) or *per os* (p.o.) were given in a constant volume of 5 (rats) or 20 (mice and gerbils) ml/kg.

References

- Griebel et al. (2001) *J. Pharmacol. Exp. Ther.* **298**:753-68.
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- Simiand J et al. (1992) *Eur. J. Pharmacol.* **219**:193-201.
- Stemmelin et al. (2004) *Eur. Neuropsychopharmacol.* **14(S3)**: S224.

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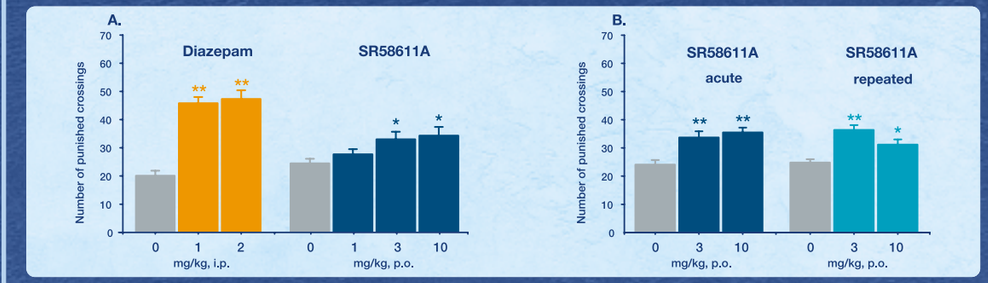
Results

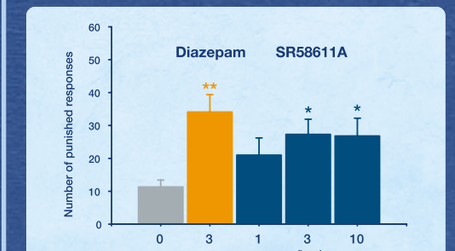
CLASSICAL MODELS OF ANXIETY

Figure 1 EFFECTS OF SR58611A AND DIAZEPAM IN THE GERBIL 4-PLATE TEST



Each bar represents the mean (+ SEM) number of punished crossings during a period of 1 min. The drugs were administered 60 minutes prior to testing (A) or during 7 days and 60 minutes prior to testing (B). *P<0.05; ** P<0.01 versus vehicle, Dunnett's test.

Figure 2 EFFECTS OF SR58611A AND DIAZEPAM IN THE RAT VOGEL CONFLICT TEST



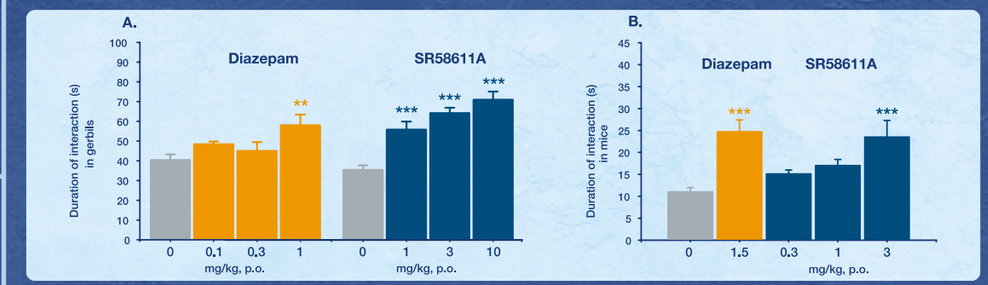
Each bar represents the mean (+ SEM) number of punished responses during a period of 5 min. The drugs were administered 30 minutes prior to testing.
*P<0.05; ** P<0.01 versus vehicle, Dunnett's test.

Table 1 EFFECTS OF SR58611A AND DIAZEPAM IN THE RAT ELEVATED PLUS-MAZE TEST

Compound	Dose mg/kg, p.o.	% Time Open Arms	% Entries Open Arms	Closed Arms Entries
• SR58611A	0	1.38 ± 0.68	3.69 ± 1.41	9.46 ± 0.54
	0.1	5.50 ± 2.14	11.00 ± 3.20	9.64 ± 0.66
	0.3	11.14 ± 1.88**	21.36 ± 3.18**	8.78 ± 0.73
	1	9.50 ± 2.38*	17.43 ± 3.63**	9.43 ± 0.77
• Diazepam	3	11.92 ± 2.40**	24.57 ± 3.91**	8.36 ± 0.44

Data represent mean ± S.E.M. The drugs were administered 60 minutes prior to testing. * P<0.05; ** P<0.01, Dunnett's test.

Figure 3 EFFECTS OF SR58611A AND DIAZEPAM IN THE SOCIAL INTERACTION TEST IN GERBILS AND MICE



Each bar represents the mean (+ SEM) duration of interaction (in seconds) during a period of 4.30 min in gerbils (A) and 5 min in mice (B). The drugs were administered 60 minutes prior to testing. ** P<0.01, ***P<0.001 Dunnett's test.

SR58611A increased the number of punished line crossings in the gerbil 4-plate test, the number of punished responses in the Vogel conflict test, exploration time of open arms in the elevated plus-maze in rats without affecting motor activity and the increased duration of social contacts in the social interaction test in gerbils and mice, indicating that SR58611A displayed robust anxiolytic-like effects in classical models of anxiety.

MODELS OF ANXIETY BASED ON A CONFRONTATION WITH A PREDATOR OR AN AGGRESSIVE RESIDENT

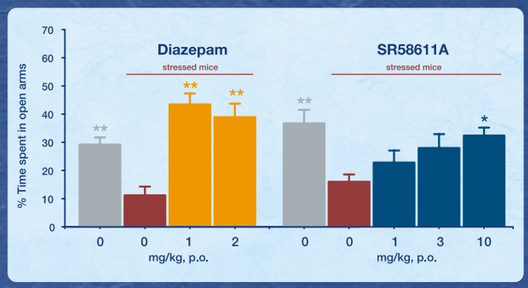
Table 2 EFFECTS OF SR58611A AND DIAZEPAM ON SEVERAL BEHAVIORAL RESPONSES DISPLAYED BY MICE BEFORE (LINE CROSSINGS) AND DURING (AVOIDANCE DISTANCE, CHASE SPEED, NUMBER OF STOPS, A/W, UPRIGHT POSTURES AND BITINGS) EXPOSURE TO A LONG EVANS RAT IN THE MOUSE DEFENSE TEST BATTERY.

		Activity		Flight	Risk assessment		Defensive reactions	
Compound	Dose (mg/kg p.o.)	Line crossings	Chase speed (m/s)	Avoidance distance (cm)	Stops	A/W	Upright postures	Bitings
• SR58611A	0	119.5 ± 6.31	0.72 ± 0.05	129.1 ± 12.4	9.28 ± 0.28	0.00 ± 0.00	2.85 ± 0.14	2.71 ± 0.18
	0.3	124.1 ± 7.08	0.59 ± 0.06	141.2 ± 15.7	8.12 ± 0.23	0.00 ± 0.00	2.00 ± 0.38	1.37 ± 0.46**
	1	110.6 ± 6.43	0.61 ± 0.06	112.0 ± 19.6	6.62 ± 0.42**	0.37 ± 0.26	1.25 ± 0.37**	0.25 ± 0.16**
	3	108.4 ± 7.56	0.60 ± 0.07	76.3 ± 14.4*	5.71 ± 0.36**	1.28 ± 0.47**	0.86 ± 0.40**	0.28 ± 0.28**
• Diazepam	0	111.7 ± 7.07	0.66 ± 0.20	169.7 ± 10.8	7.55 ± 0.53	0.11 ± 0.11	2.89 ± 0.11	2.55 ± 0.29
	0.3	112.9 ± 7.72	0.54 ± 0.14	163.7 ± 16.7	6.50 ± 0.72	0.10 ± 0.10	2.20 ± 0.33	2.20± 0.33
	1	134.7 ± 8.49	0.53 ± 0.06	120.5 ± 18.9*	4.18 ± 0.72**	0.63 ± 0.20	2.10 ± 0.28	1.81 ± 0.35
	3	104.8 ± 8.63	0.46 ± 0.15	87.3 ± 20.0**	1.60 ± 0.56**	1.70 ± 0.45**	1.00 ± 0.33**	0.90 ± 0.31**

A/W = approaches followed by avoidances responses

Data represent mean ± SEM. SR58611A and diazepam were administered 60 min before testing. * P<0.05; ** P<0.01 Dunnett's or Dunn's test.

Figure 4 EFFECTS OF SR58611A AND DIAZEPAM IN THE MOUSE SOCIAL DEFEAT STRESS PARADIGM



Each bar represents the mean (+ SEM) percentage time spent in the open arms of the elevated plus-maze test during a period of 4 min. Mice stressed by a 60 min exposure to an aggressive resident were compared to unstressed controls. The drugs were administered 90 min prior to testing. *P<0.05; ** P<0.01 versus stressed vehicle, Dunnett's test.

SR58611A decreased risk assessment, flight and potently reduced defensive threats and attacks in the mouse defense test battery without affecting motor activity. Moreover, SR58611A fully counteracted the decrease in exploratory behavior induced by a social defeat stress in mice suggesting that SR58611A displayed anti-anxiety effects in unescapable and highly stressful situations.

SUMMARY OF THE EFFECTS OF SR58611A IN MODELS OF ANXIETY. COMPARISON WITH DIAZEPAM.

	Models of anxiety									Side effects				
	4-plate	Vogel conflict	Plus maze	Social interaction	Social interaction	Defense battery Flight	Defense battery Risk	Defense battery Aggresssion	Social defeat	Rotarod	Rotarod with ethanol	Withdrawal-induced anxiety	Episodic memory Object recognition	Spatial memory Water maze
• Species	gerbil	rat	rat	mouse	gerbil	mouse	mouse	mouse	mouse	mouse	mouse	mouse	rat	rat
• SR58611A	3/3*	(3)	0.3	3	1	3	0.3	0.3	10	>100	>10	(>10)*	>30*	>10*
• Diazepam	1	(3)	3	1.5	0.1	1	1	3	2	10	3	(5)*	3*	(3)*

*MED: p.o. or (i.p.) * repeated treatment*

Conclusion

- **The potent and selective β_3 adrenoceptor agonist SR58611A was able to reduce anxiety-related responses in several animal models. The drug showed a broad range of efficacy in classical models of anxiety and in tests of unavoidable stress exposure. Moreover, SR58611A was devoid of adverse side effects classically observed with benzodiazepines. These findings suggest that SR58611A may have beneficial effects on anxiety-related behaviors, strengthening further the therapeutic value of the β_3 adrenoceptor agonist, which was shown to have a strong potential for the treatment of major depression (Simiand et al., 1992, Stemmelin et al., 2004).**