Anxiolytic-like but not antidepressant-like activity of Lu AF21934, a novel, selective positive allosteric modulator of the mGlu4 receptor

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INTRODUCTION

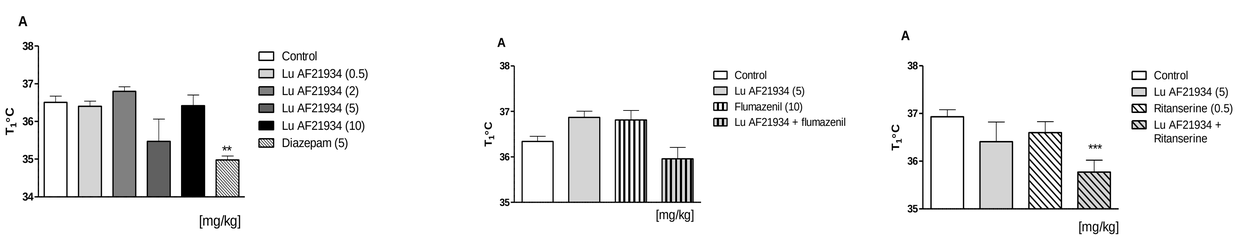
Depression and/or anxiety are among the most common psychiatric disorders. Glutamatergic system, the main excitatory system in the brain, is a promising target of a novel antidepressant and anxiolytic therapy. Anxiolytic effects can be achieved by the blokade of glutamatergic neurotransmission as its hyperfunction can occur in anxiety.

Earlier studies showed that Group III mGlu receptors-preferred orthosteric agonist, LSP1-2111 produced anxiolytic-like but not antidepressant-like effects upon peripheral administration. Herein, we report that the pharmacological actions of Lu AF21934, a novel, selective and brain-penetrant positive allosteric modulator (PAM) of the mGlu4 receptor in the stress-induced hyperthermia (SIH), the four-plate and the marble-burying tests.

RESULTS

In all models a dose dependent anxiolytic-like effect of Lu AF21934 was seen, which was inhibited by the benzodiazepine receptor antagonist flumazenil and was not serotonin-dependent, as it persisted in PCPA-treated mice, and was not influenced by the blockade of either 5-HT_{1A} receptors by WAY 100645, or 5-$HT_{2A/2C}$ receptors by ritanserin.

SIH Test



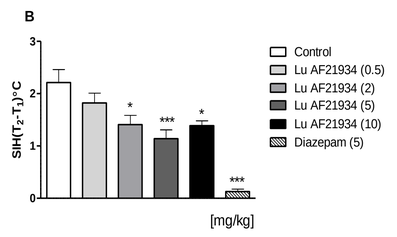


Fig. 1 The effect of Lu AF21934 on the core body temperature (A) and the SIH response (B) n=8-10 mice*p<0.05 and ***p<0.001 versus control group.

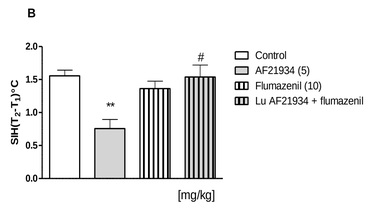


Fig.2 The effect of combined administration of Lu AF21934 and flumazenil on the core body temperature (A) and the SIH response (B). n=8-10 mice **p<0.001 versus control group and #p<0.05 versus Lu AF21934 treated.

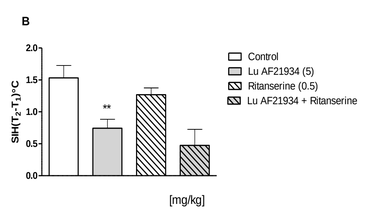


Fig. 3 The effect of combined administration of Lu AF21934 and ritanserin on the core body temperature (A) and the SIH paradigm (B). n=8-10 mice**p<0.01 and ***p<0.001 versus control group.

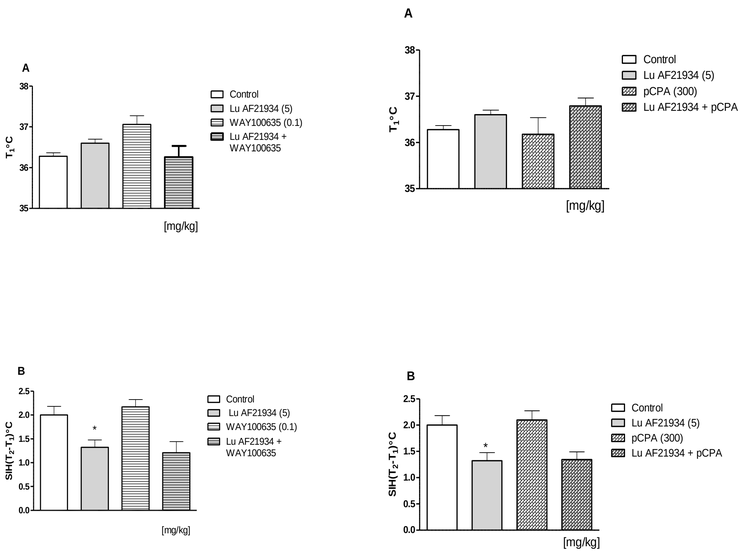


Fig. 3 The effect of combined administration of Lu AF21934 and WAY100635 on the core body temperature (A) and the SIH response (B). n=8-10 mice *p<0.005 versus control group.

Fig. 4 The effect of Lu AF21934 in 5-HT depleted mice on the SIH paradigm in singly-housed mice, on the core body temperature (A) and the SIH response (B). n=8-10 mice *p<0.005 versus control group.

MATERIALS and METHODS

Stress-induced hyperthermia. The animals were housed individually 24 h before testing. The body temperature was measured for each mouse at t = 0 min (T1) and t = +15 min (T2). Albino Swiss mice were placed into a new cage immediately following T1, with the difference in temperature (T2-T1) used as the measure of stress-induced hyperthermia. A comparison between T1 in vehicle-treated mice and those administered with test compound was used to determine whether the agent affects the body temperature alone

Marble-burying - mice were individually placed in transparent, polycarbonate cages containing a 5-cm layer of sawdust and 24 glass marbles (1.5 cm in diameter) evenly spaced against the wall of the cage. Thirty minutes later, the animals were removed from the cages and the number of marbles at least two-third buried in the sawdust was recorded.

Four-plate test - studies were conducted using a box made of opaque plastic and rectangular in shape (24 × 16 × 17 cm). The floor was covered with four rectangular metal plates (10 × 6 cm), separated by a 4-mm gap. The plates were connected to the source of continuous current, which enabled a 120 V potential difference between two adjacent plates for 0.5 s once the experimenter pressed the switch. Mice (Albino Swiss) were gently placed into the box and allowed to explore for 15 s. Then, each time a mouse passed from one plate to another, the experimenter electrified the whole floor thus evoking a visible flight reaction of the animal. If the animal continued running, no new shock was delivered for the following 3 s. Punished crossings were counted for 60 s

Tail suspension test Immobility was induced by tail suspension according to the procedure of Steru (Steru *et al*., 1985). C57BL/6J mice were hung individually on a plastic string 75 cm above the table top with an adhesive tape placed roughly 1 cm from the tip of the tail. The immobility duration was recorded for 6 min. The mice were considered immobile only when they hung passively.

Four-plate

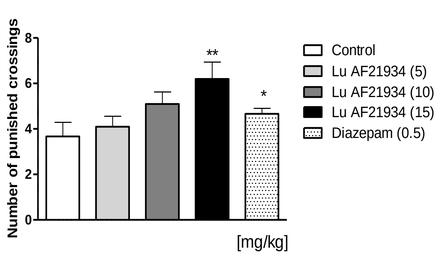


Fig.5 The effect of Lu AF21934 in punished crossing in four-plate test Drugs were given 60 min before test. n=8-10 mice. *p<0.05, **P<0.01 versus control group.

Marble-burying

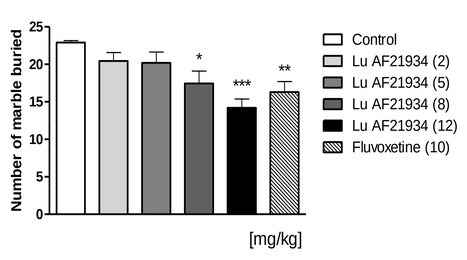


Fig. 6 Effect of Lu AF21934 on marble burying behaviour. n=8-10 mice.*p<0.05 and ***p<0.001 versus control group.

Tail-suspension

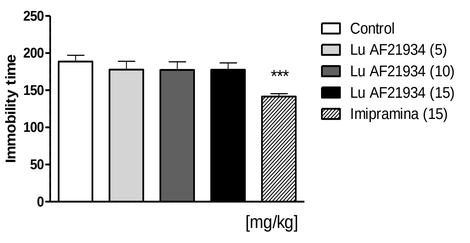


Fig. 7 The effect of Lu AF21934 on the immobility time in tail suspension test. n=8-10 mice. ***p<0.001 versus control group.

CONCLUSSION

These results suggest that the GABA-ergic system but not the serotonergic system is involved in the mechanism of the anxiolytic-like phenotype of Lu AF21934 in rodents.

There is no conflict of interest