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

Sławińska A, Wieronska J M, Stachowicz K, Palucha-Poniewiera A, Uberti M A, Bacolod M D, Doller D, Pile A

Institute of Pharmacology, Polish Academy of Sciences, Smogora 12, 31-343 Krakow, Poland

Lundbeck Research USA, 215 College Road, Paramus, NJ 07652, USA

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 blockade 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-HT1A receptors by WAY 100645, or 5-HT2A/2C receptors by ritanserin.

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.

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