Pharmacological characterisation of EVT 101, a novel potent and orally acting NR2B subtype selective NMDA antagonist

A. M. CESURA, A. EBNETH1, VON DER KAMMER1, E. PINARD2, G. JAESCHKE2, J. A. KEMP1
1Evotec AG, Hamburg, Germany; 2Hoffmann-La Roche Ltd, Basel, Switzerland

Introduction
The glutamate gated NMDA ion channels play key roles in excitatory synaptic transmission (Kemp & McKernan, 2002). NMDA receptors are associated with numerous neurological disorders, and, thus, NMDA receptor antagonists, particularly those selectively targeting the NR2B subunit, are of considerable therapeutic interest for the treatment of several conditions, including Alzheimer’s disease and pain (Preskorn et al., 2008). Whereas non-selective NMDA receptor antagonists have a therapeutic window between their therapeutic action and mechanism based side-effects, both pre-clinical as well as initial clinical experience indicate that NR2B subtype-selective NMDA antagonists are better tolerated and do not produce the profound CNS adverse effects typical of non-selective NMDA blockers. While several NR2B antagonists have been developed, few of them have suffered from lack of oral bioavailability or off-target effects which have precluded their development. In this report, we describe the in vitro and in vivo properties of EVT 101, a potent and orally bioavailable NR2B receptor antagonist currently under clinical development for treatment-resistant depression.

Methods

In vitro studies

Binding. [3H]MK-801 and [3H]Ro 25-681 binding to rat brain membranes was performed as described in Gill et al., 2001, and Mutel et al., 1998. Electrophysiology. CHO-K1 cells were transiently transfected with the cDNA clones encoding the human NR1 subunit of the NMDA receptor (GRIN1) and with plasmids encoding the NR2A (GRIN2A) or NR2B (GRIN2B) subunit. Patch-clamp experiments were performed in the voltage-clamp mode and whole-cell currents recorded. Currents were elicited by application of 100 µM NMDA and 30 µM glycine.

In vivo studies

Ex vivo binding: NR2B receptor occupancy was determined in mice after oral administration of EVT 101 by ex vivo binding after i.v. administration of [3H]MK-801 as described by Murray et al., 2000.

Protection from NMDA-induced seizures. EVT 101 was administered to mice 15 min (i.v.) and 30 min (p.o.) administration, respectively, before i.c.v. injection of NMDA (0.15 mg/kg, Gill et al., 2002) and animal observed for 5 min.

Motor Coordination and locomotor activity. Motor coordination was studied in mice using a Rotarod apparatus. EVT 101 was given i.v. or p.o. 15 or 30 min, respectively, before the test and the latency time to fall off the Rotarod was determined. Locomotor activity was studied in rats over a 4 h period after i.p. administration of EVT 101 (Gill et al., 2002).

ADME
ADME in vitro and in vivo experiments were performed according to international Standard Operating Procedures (SOPs). The results were expressed as the mean ± S.E.M.

ADME properties
In rats, EVT 101 was rapidly and extensively absorbed after oral administration with a good bioavailability (F > 100%). Clearance after i.v. and p.o. was 24 and 19 mL/min/kg respectively with a Vd of 90 mL/kg. PK parameters of EVT 101 after oral administration in various species including humans:

Species | Oral bioavailability | Vd (L/kg) | Cmax (µg/mL) |
---|---|---|---|
Rat | 100 | 0.9 | 50 |
Dog | 90 | 1.2 | 50 |
Monkey | 85 | 0.8 | 50 |
Human | 75 | 0.3 | 50 |

Conclusions
EVT 101 is a potent antagonist at NR2B receptors containing the NR2B subunit with no significant off-target activities. EVT 101 is orally active in vivo models without inducing effects on motor coordination or activity typical of non-selective NMDA receptors antagonists. EVT 101 has good PK properties and oral availability making it suitable for once-a-day oral dosing in humans. EVT 101 has successfully completed extensive toxicity studies and PhI clinical trials and is currently in a PhII proof-of-concept trial in treatment-resistant depression.

References
Furukawa Y. et al. (2006) Pharmacological characterisation of the NMDA receptor antagonist, EVT 101, a novel non-competitive, non-selective NMDA receptor antagonist. Neuropharmacology. 50:1806-1812
Furukawa Y. et al. (2007) Pharmacological characterisation of the NMDA receptor antagonist, EVT 101, a novel non-competitive, non-selective NMDA receptor antagonist. Neuropharmacology. 52:1806-1812
Furukawa Y. et al. (2007) Pharmacological characterisation of the NMDA receptor antagonist, EVT 101, a novel non-competitive, non-selective NMDA receptor antagonist. Neuropharmacology. 52:1806-1812