AR-R15896AR - A Low Affinity Use Dependent NMDA Antagonist for Stroke - A Preclinical Review

Gene C. Palmer

AstraZeneca R & D, Rochester, NY

The low affinity use dependent NMDA receptor antagonists have advanced to clinical trials because of the wider safety margins between doses eliciting side effects and efficacy; a contrast to the high affinity competitive or use dependent compounds. Under \textit{in vitro} conditions the affinity of [S]-AR-R15896AR for the ionic channel site associated with the NMDA receptor is 1.3 \(\mu\)M compared to the prototypic high affinity compound, MK801 (IC\(_{50}\) = 14 nM). In further work, AR-R15896AR effectively prevented mechanisms associated with NMDA-induced cell death when tested in various preparations of neuronal cultures. Under \textit{in vivo} conditions AR-R15896AR prevented convulsions and mortality in response to an NMDA challenge in mice, as well as protected striatal neurons from the toxic consequences of malonic acid in the rat. In a variety of investigations with stroke models AR-R15896AR was shown to protect: 1) The rodent and feline brain from transient focal ischemia, 2) The rodent brain from global ischemia and/or anoxia, and 3) The rodent brain from permanent focal ischemia. Following toxicology evaluations, AR-R15896AR entered clinical trials and in Phase I was found to be well tolerated in humans. Phase II trials for patients with acute stroke are underway.