Effect of Subtype-Selective NMDA Receptor Antagonists On Retinal Spreading Depression

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Spreading depression (SD) is a temporary disruption of local ionic homeostasis that propagates slowly across the cortex. SD contributes to the initiation of migraine attack and lesion progression in experimental stroke. NMDA receptor antagonists are known to be the most effective drugs to suppress SD. So far, NMDA receptor antagonist are still perceived as unlikely candidate as anti-SD drug in humans because of their unacceptable side effects, but the NMDA-receptor antagonist, memantine is now used chronically in elderly for Alzheimer's and epilepsy patients and some subtype selective receptor antagonists may well be effective with reduced side effects. The aim of this study was to determine whether NR2A, NR2B and NR2D selective NMDA receptor antagonists suppress SD in the chicken retina preparation in comparison with the non-competitive NMDA receptor antagonist, MK801.

Fifteen SD episodes were elicited by ejection of 0.1M KCl in each experiment. Image acquisition was started as each SD was initiated, and carried out for 3 minutes. Three separate SD were elicited for each of the different tests: (i) initial Ringer's control; (ii) low concentration; (iii) medium concentration; and (vi) high concentration of vehicle or drug; (v) post-treatment Ringer's control. A recovery of 15 min followed each SD elicitation, and the drug-syringe was changed immediately after the third recording of each test to ensure adequate perfusion of a drug or Ringer's condition for the following test.

MK801 significantly suppressed the area under the curve (AUC) of SD, but not the propagation rate. Both the NR2B preferring (R0 25 25-6981 and CP,101-606) and NR2D preferring receptor antagonists (UBP141), did not significantly alter retinal SD, although a reduced AUC of SD to 38.9% was observed with R0 25 25-6981 at 10 µM (p>0.05 compared with control group, n=8). Surprisingly, the NR2A preferring receptor antagonist, NVP-AAM077, markedly reduced both the area under the curve (AUC) of SD and propagation rate in a concentration dependent manner. At 0.3 µM, the AUC and propagation rate of SD reduced to 31.5 % and 52.5% respectively (n=7; p<0.01). The extent of SD suppression on AUC is similar to that of MK801 at 10 µM. Differently from that of MK801, the effect of NVP-AAM077 on SD is reversible after the drug withdrawal (p<0.05, the 5th test versus the 4th test). Our results suggested NR2A, but to a less extent to NR2B, are key mediators of SD, indicating potential therapeutic benefit for NR2A-preferring antagonist to treat SD-related neurological diseases, e.g. migraine.