Poster 558.03

Presented at the Annual Meeting
Society for Neuroscience
November 2017
Washington DC, Maryland

Influence of species differences at NMDA receptors pharmacology

D. Bertrand[1], S. Bertrand[1], E. Neveu[1], K. Kambara[1] and M. Ackley[2]
[1]HiQScreen, 6 rte de Compois, 1222 Vésenaz, Geneva, Switzerland. [2]SAGE Therapeut., Cambridge, MA, USA

Introduction

- Development of novel molecules acting at the NMDA receptors necessitate the identification of pharmacologically active compounds at human NMDA receptors but also their characterization in different animal models that are used in preclinical efficacy and safety studies.
- We recently reported that the endogenous oxysterol, 24(S)-hydroxycholesterol (24(S)-HC) directly modulates the NMDA-R and positively impacts plasticity in the hippocampus (Paul *et al*, 2013).
- Subsequently, we have developed novel synthetic positive modulators of NMDA-R and two representative preclinical tool compounds are SGE-301 and SGE-550
- In the present study we have examined the functional properties of NMDA receptors reconstituted by expression of the GluN1a and GluN2A subunits from human, dog, rat and mouse and compared their pharmacological properties.

Sequence alignment across species

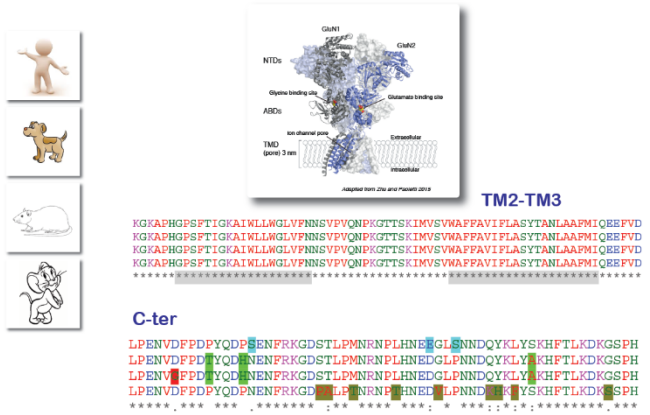

Figure 1. Sequence alignments of the human, dog, rat and mouse GluN1 and GluN2A indicate that while some regions of the receptors are highly conserved notable differences can be observed in other segments of the proteins.

Agonist Concentration-Responses

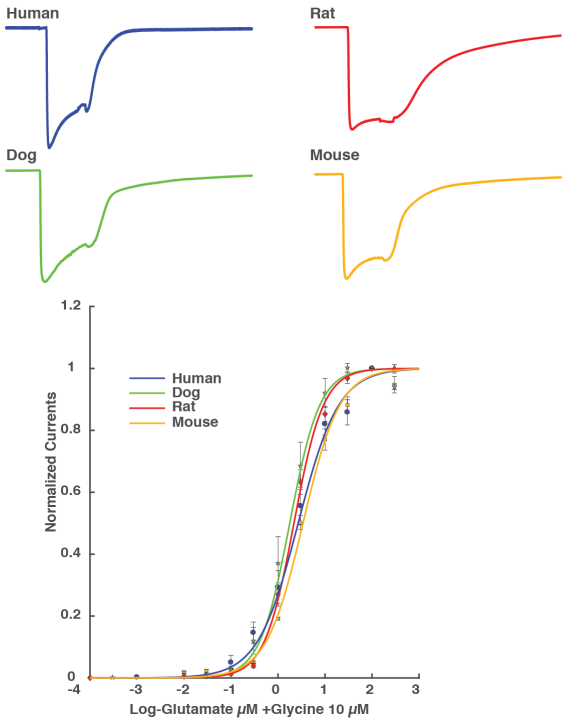

Figure 2. Oocytes were injected with mRNA for human, dog, rat and mouse GluN1 and GluN2A subunits. Increasing concentrations were applied in the presence of 10 µM Glycine. A similar sensitivity to glutamate was observed across all species

Modulation by PAMs

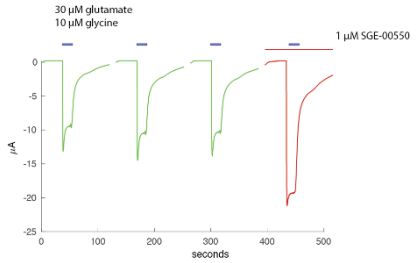

Figure 3. Currents were evoked using 30M Glutamate and 10 µM Glycine in the absence and presence of PAM and PAM CRCs were constructed

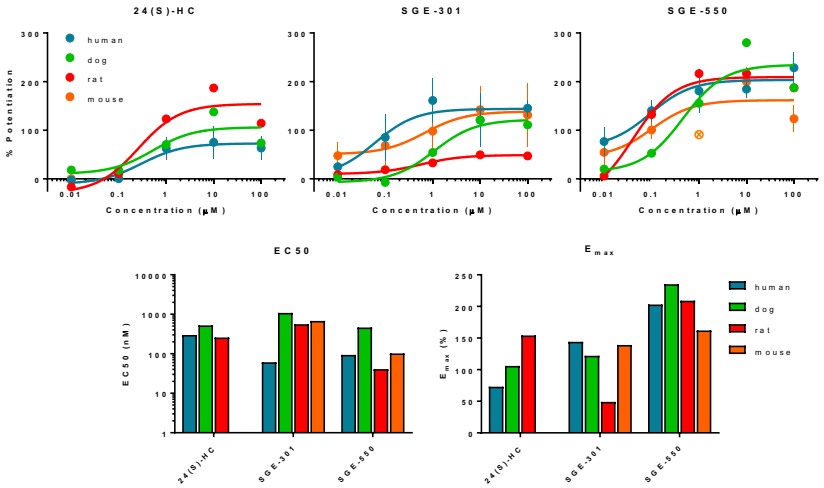

Figure 4. Receptors display differential sensitivity to allosteric modulators 24(S)-HC, SGE-301 and SGE-550

Conclusions

These data highlight the importance of fully characterizing the activity of novel NMDA receptor modulators across species that will be used in preclinical efficacy and safety models in order to better understand pharmacokinetic-pharmacodynamic relationships.