Hemodynamic response from Ketamine and effect of mGluR2/3 agonist (LY404039) pretreatment.

A. Andersson[1], M. Lindberg[1], F-H. Wang[1], and T. Klason[1]
[1]AstraZeneca R&D, Sodertalje, Sweden

Introduction:

Pharmacological MRI (phMRI) is a growing field in both academic research and drug discovery. The ability to detect brain activation via changes in the hemodynamic response (HDR) is important for the investigation of brain active compounds. In neuroscience research a number of CNS-active compounds have been investigated by MRI in both rodent models (ref. 1, 2) and in humans (ref. 3). The possibility to detect brain activation in both rodents and humans makes phMRI a valuable technique for translational science, gaining confidence through pre-clinical studies to proceed towards the clinical development of a drug.

N-methyl-D-aspartate (NMDA) receptor antagonists such as Ketamine have been used at subanesthetic doses to produce schizophrenic-like phenotypes in animal and man (ref. 4). The behavioral effects in such models have been shown to be attenuated by selective mGluR2/3 agonists, e.g. LY404039 (ref. 5). However, little is known about the blocking effect of these compounds on Ketamine-induced brain activation patterns, which could be useful as a translational biomarker.

Therefore, the current study aimed at determining the effect of an mGluR2/3 agonist (LY404039) on Ketamine-induced HDR in rat brain using phMRI.

Materials and Methods:

Two groups of eight 225-300 gram male Sprague Dawley rats maintained under isoflurane anesthesia were used for these experiments. A Bruker 9.4T MRI system and a single shot SE EPI-sequence (TE=50 ms, TR=4 s) with a matrix size of 85x128 / FOV 20x30 mm were used to acquire phMRI data. The geometrical setup was 9 one millimeter thick axial slices, covering a total of 13 mm. The USPIO Resovist™ was used as a contrast agent.

The animals were administered LY404039 (3 mg/kg) or vehicle (saline) subcutaneously (s.c.) 5 minutes before and Resovist™ (i.v.) 5 minutes after the phMRI experiment started. Twenty minutes after the contrast agent administration (i.e. 30 minutes after pretreatment), Ketamine (25 mg/kg, s.c.) was given. The hemodynamic response was calculated from the equation given by Mandeville (ref. 6). Quantification of the activation was calculated through an area-under-the-curve for the HDR time-course during the first 15 minutes after Ketamine injection, which we define as the total hemodynamic response (tHDR). Two different ROI's in different brain regions, thalamus and hippocampus, were evaluated for each animal.

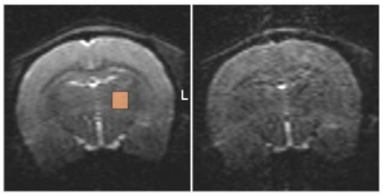


Fig. 1: EPI images before contrast agent Administration on the left and after on the right. The Region of interest (Thalamus) is outlined on the left Image. A head surface coil was used for signal detection.

Results:

Early studies indicated that Ketamine gave the largest hemodynamic responses in our setup in Thalamus and Hippocampus, areas that were chosen for further investigation of the effect of pretreatment with the mGluR2/3 agonist LY404039 (data not shown). In figure 2, the hemodynamic response curve from Thalamus is shown. The Ketamine injection is outlined in the figure and the response from about 3 minutes to the end of the experiment is shown, which is 30 minutes after Ketamine injection. Pretreatment with LY404039 was able to significantly block the Ketamine response, as shown both in the HDR graph and the integrated response in fig 3.

Fig. 2:Thalamus: hemodynamic response

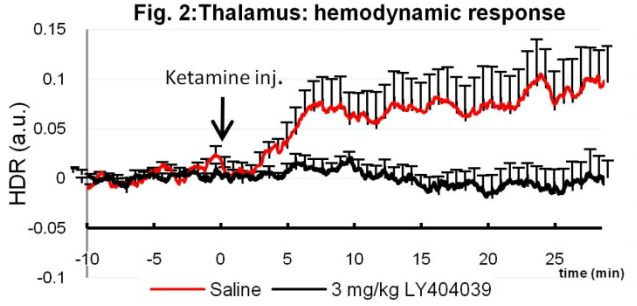
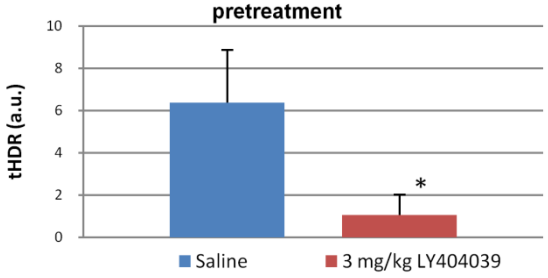


Fig. 3: tHDR Thalamus, Saline vs LY404039 pretreatment



Discussion and Conclusions:

The current results clearly demonstrates that a selective mGluR2/3 receptor agonist, LY404039, attenuates Ketamine induced HDR in relevant brain regions. These findings support the use of this model for testing of potential new drugs for schizophrenia in a pre-clinical setting as well as a translational tool for human clinical studies.

References:

1. Gozzi et al. Neuropsychopharmacology (2006) 31, 1690-1703
2. Littlewood et al. Psychopharmacology (2006) 186, 64-81
3. Rose et al. Magnetic Resonance in Medicine (2006) 55, 9-15
4. Aghajanian, Psychopharmacology (2009) 206, 575-585
5. Rorick-Kehn et al. Psychopharmacology (2007) 193, 121-136
6. Mandeville et al. Magnetic Resonance in Medicine (1998) 39, 615-624