V1a antagonism normalizes a social brain network in valproate rat model of autism revealed by functional MRI

Thomas Mueggler1, Dany D’Souza2, Barbara Biemans1, Andreas Bruns1, Basil Künnecke1, Patrick Schneider1, Christophe Grundschobert1, and Markus von Kienlin1

Pharma Research & Early Development, DTA Neuroscience, Hoffmann-La Roche, Basel, Basel-City, Switzerland, Pharma Research & Early Development, Small Molecule Research, Hoffmann-La Roche, Basel, Basel-City, Switzerland

TARGET AUDIENCE: The presented data are of interest for scientists and clinicians involved in imaging and/or drug development with focus on neurodevelopmental disorders.

PURPOSE: Vasopressin, akin to oxytocin, is a neuropeptide thought to play an important role in regulating social behavior. Here, we investigated the role of vasopressin in the rat valproate (VPA) model of autism presenting autistic-like behaviors including social behavior deficits, increased repetitive behavior, sensory dysfunction and deficits in communication2,3. The aim was to identify a potential imaging endophenotype in the VPA rat model and, by making use of a potent, selective, brain-penetrant vasopressin receptor 1a (V1a) antagonist, to test the role of the V1a receptor in this particular animal model.

METHODS: The animal model used was previously described in detail4. Pregnant Wistar rats received a single intra-peritoneal dose of 600 mg/kg VPA (Sigma, UK) on gestational day 12.5 (ET12.5). Control dams received an injection of saline at ET12.5. The study was conducted in male VPA-exposed offspring (VPA, n=8) with tail malformation and control animals (WT, n=21, WT & VPA w/o tail malformation). Group allocation was done by presence of a tail kink5, a postnatal malformation used to confirm successful exposure to the teratogenic actions of VPA during gestation6. After assessment of baseline imaging (ASL-perfusion MRI, rs-fMRI) at post-natal day 60 (p60) animals were subjected to a 7-day chronic treatment either with V1a antagonist (RO, Hoffmann-La Roche, 90 mg/kg, daily, oral or vehicle (VEH)). At day 8, 24h after last dosing, animals underwent MRI follow-up assessment (ASL-Perfusion MRI). For imaging rats were sedated using a s.c. infusion of medetomidine (0.1mg/kg) following a priming bolus of 0.2mg/kg. MRI was carried out on a Bruker BioSpec 9.4T system equipped with a 72 mm bird-cage resonator for excitation and a surface coil for reception. Perfusion MRI was obtained using a protocol described earlier8. Briefly, continuous arterial spin labelling (CASL) with centred-RARE readout (TR/TE = 3000ms/5.7ms, RARE factor = 32, FOV = 4cm x 4cm, 128 x 64 matrix, 1mm slice thickness, 2 slices, 2.5s labelling, 0.4s post labelling delay). For subsequent registration to an anatomical template with an associated atlas defining 62 regions of interest (ROIs), T2-weighted anatomical RARE images were acquired. Perfusion values for each ROI were normalized slice-wise to brain mean perfusion to derive region-specific values independent of inter-individual differences of the animals’ global hemodynamic status. ROI-wise differences between the groups were tested for significant effects using univariate statistics (ANOVA, post-hoc). Rs-fMRI data were acquired using a T2*-weighted single shot gradient echo EPI sequence (TR/TEff=2000/17.5ms; 128x128 matrix; 32x32mm2 FOV; 20 coronal slices; 1mm thickness). Two scans of 165 EPI volumes were acquired per subject. EPI data were preprocessed in FSL v5.0 (steps: brain extraction, motion correction, high-pass filter >0.007 Hz, regression of motion parameters). A group-level permutation test was performed to determine an overall significance level of 0.05.

RESULTS AND DISCUSSION: Compared to WT, offspring of VPA-exposed rats, assessed at P60, are characterized by a significantly altered regional perfusion in sensory and perirhinal cortex, superior and inferior colliculi, hippocampus, hypothalamus, ventral tegmental area (VTA) and dorsal striatum (Fig.1). Supplementary discriminant analysis in the feature space spanned by the ROIs corroborated group allocation based on the characteristic tail kink. The main differences in FC between VPA and WT rats were observed between VTA and sensory cortices (decreased FC) as well as between motor and sensory cortices and several striatal regions (CPu, Nacc), globus and ventral pallidium (GP, VP) and inferior and superior colliculi (increased FC) (Fig.2). One week of chronic treatment with V1a antagonist RO normalized some of the perfusion difference present at baseline, specifically in dorsal striatum, VTA and superior colliculus in the VPA group with no compound effect in WT rats (Fig.3). The only other region which showed a significant difference between VEH and RO90 in the VPA group was the inferior colliculus. No effect of 7 day chronic treatment was observed in the hippocampus (data not shown). Due to the small differences in FC at baseline and the limited group size (VPA group split in 2 groups), differences in FC at baseline and between VPA and WT were investigated if there were any differences of the FC values between VPA and control rats.

CONCLUSION: Our results demonstrate a functional phenotype in VPA rats with altered perfusion as a surrogate of disturbed neural activity in brain regions implicated in social behavior. Data from treatment study are indicative of an overactive vasopressin neurotransmission in the VPA model of autism and suggest that V1a antagonists have the potential to improve core symptoms of autism such as social interaction for which there is currently no drug treatment.