Metabotropic glutamate receptor 5

Metabotropic glutamate receptor 5 is a G protein-coupled receptor that in humans is encoded by the GRM5 gene.

Surgical specimens from patients with mesial temporal lobe epilepsy (MTLE) show abnormalities in tissue concentrations of metabotropic glutamate receptor 5 (mGluR5). To clarify whether these abnormalities are specific to the epileptogenic zone (EZ), Lam et al. characterized in vivo whole-brain mGluR5 availability in MTLE patients using positron emission tomography (PET) and [11 C]ABP688, a radioligand that binds specifically to the mGluR5 allosteric site.

Thirty-one unilateral MTLE patients and 30 healthy controls underwent [11 C]ABP688 PET. They compared partial volume corrected [11 C]ABP688 non-displaceable binding potentials (BPND) between groups using region-of-interest and whole-brain voxel-wise analyses. 18 Ffluorodeoxyglucose (FDG) PET was acquired in 15 patients, for whom we calculated asymmetry indices of [11 C]ABP688 BPND and [18 F]FDG uptake to compare lateralization and localization differences.

[11 C]ABP688 BPND was focally reduced in the epileptogenic hippocampal head and amygdala ($p<0.001$). Patients with hippocampal atrophy showed more extensive abnormalities including the ipsilateral temporal neocortex ($p=0.006$). [11 C]ABP688 BPND showed interhemispheric differences of higher magnitude and discriminated the epileptogenic structures more accurately when compared to [18 F]FDG uptake, which showed more widespread hypometabolism. Amongst 23/25 operated patients with > 1 year follow-up, 13 were seizure-free (Engel Ia), and showed significantly lower [11 C]ABP688 BPND in the ipsilateral entorhinal cortex.

[11 C]ABP688 PET provides a focal biomarker for the EZ in MTLE with higher spatial accuracy compared to [18 F]FDG PET. Focally reduced mGluR5 availability in the EZ might reflect receptor internalization or conformational changes in response to excessive extracellular glutamate, supporting a potential role for mGluR5 as therapeutic target in human MTLE [1)].

[11 C]ABP688 is a positron emission tomography (PET) radioligand that binds selectively to Metabotropic glutamate receptor 5s (mGluR5). The use of this tracer has identified receptor binding changes in clinical populations, and has been informative in drug occupancy studies. However, previous studies have found significant increases in [11 C]ABP688 binding in the later scan of same-day comparisons, and estimates of test-retest reliability under consistent scanning conditions are not available. The objective of a study of Smart et al., was to assess the variability of [11 C]ABP688 binding in healthy people in scans performed at the same time of day.

Two [11 C]ABP688 scans were acquired in eight healthy volunteers (6 women, 2 men) using a high-resolution research tomograph (HRRT). Scans were acquired 3 weeks apart with start times between 10:00am and 1:30pm. Mean mGluR5 binding potential (BPND) values were calculated across cortical, striatal and limbic brain regions. Participants reported on subjective mood state after each scan and blood samples were drawn for cortisol analysis.

No significant change in BPND between scans was observed. Variability in BPND values of 11 to 21% was observed across regions, with the greatest change in the hippocampus and amygdala. Reliability

was low to moderate. BPND was not statistically related to scan start time, subjective anxiety, serum cortisol levels, or menstrual phase in women.

[11 C]ABP688 BPND estimates show moderate variability in healthy people. Reliability is fair in cortical and striatal regions, and lower in limbic regions. Future research using this ligand should account for this in study design and analysis [2].

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2)
Smart K, Cox SML, Nagano-Saito A, Rosa-Neto P, Leyton M, Benkelfat C. Test-retest variability of [(11) C]ABP688 estimates of metabotropic glutamate receptor subtype 5 availability in humans. Synapse. 2018 Jun 23. doi: 10.1002/syn.22041. [Epub ahead of print] PubMed PMID: 29935121.