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Serial 11C-methionine PET detects involvement of astroglia in neuroinflammation following acute myocardial infarction

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Background: Recent evidence indicates that acute myocardial infarction (MI) evokes concurrent acute cardiac and neuroinflammation. 18F-GE180 PET imaging of the translocator protein (TSPO) identified activated microglia in the brain early after MI. The amino acid 11C-methionine exhibits a low background signal in heart and brain compared to 18F-FDG, and it is known to accumulate in inflammatory cells, with an albeit different profile compared to TSPO markers.

Purpose: We aimed to evaluate the feasibility of 11C-methionine PET to image cardiac and brain inflammation following MI.

Methods: Male C57/Bl6N mice underwent permanent ligation of the left coronary artery (n=10) or no surgery (n=3). For attenuation of inflammation, a subgroup of mice were pretreated with a therapeutic antibody cocktail against integrins involved in leukocyte tracking and extravasation (anti-CD11a, -CD11b, -CD49d; 100 µg). Serial whole body 11C-methionine images were obtained at 3, 5, and 7d after surgery. Perfusion was assessed by 99mTc-sestamibi SPECT at 7d after MI. The PET signal was verified by immunohistochemistry co-staining for astrocytes (GFAP) or microglia (CD68) with the L-type amino acid transporter-1 (LAT-1) in brain tissue collected at 3 and 7d after MI.

Results: 11C-methionine uptake was elevated in the infarct region at 3d after MI compared to healthy mice (5.9±0.9 vs 2.6±0.5 %ID/g; p<0.01), receding by 7d after surgery (4.3±0.6 %ID/g; p=0.03 vs 3d). A parallel increase in 11C-methionine uptake was identified in whole brain early after MI, with highest signal at 3d (2.9±0.4 vs 2.4±0.3 %ID/g; p>0.05), and returning to baseline levels at 7d. Statistical parametric mapping revealed a predominant increase of uptake in hypothalamus and dorsal thalamus regions. Anti-integrin treatment reduced 11C-methionine uptake in the heart at 3d and 7d post-MI. Interestingly, a comparable reduction in signal was observed in the brain. However, untreated animals showed smaller infarct size than the treated group (44.2±9.8 vs 59.6±4.0%; p=0.02). Brain 11C-methionine uptake directly correlated with infarct region cardiac uptake (r=0.47, p<0.05). Immunofluorescence revealed co-localization of LAT-1 and GFAP at 3d post-MI, suggesting that 11C-methionine may identify early neuroinflammatory astrocyte activity prior to microglial activation.

Conclusion: PET imaging of amino acid metabolism detected concurrent inflammation in the heart and in the brain after MI. 11C-methionine appears to identify the astrocyte response component of neuroinflammation, with earlier timecourse profile compared to microglial activation shown previously by TSPO PET. These findings support the use of whole body PET imaging with multiple inflammation markers to dissect the cellular components of inflammatory heart-brain networking.
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Figure. (A) Heart (upper) and brain (lower) 11C-methionine uptake images in control animals and at 3 days after myocardial infarction (MI) with and without anti-integrin treatment. (B) Correlation between infarct and whole brain 11C-methionine uptake. (C) Immunohistochemistry shows co-localization of astrocytes (GFAP, green) and L-amino acid transporter (LAT-1, red) in the hippocampus at 3d post-MI.