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Evaluation of the TSPO (18KDa)/PBR radioligand [^{18}F] DPA-714 in a rat model of focal cerebral ischemia

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Introduction: Focal cerebral ischemia leads to an inflammatory reaction which involves an over-expression of the translocator protein, TSPO (18KDa), that is expressed in the monocytic lineage (microglia and monocyte) and astrocytes under such situation [1]. Here, the new peripheral-type benzodiazepine receptor (PBR) tracer [^{18}F] DPA-714 was evaluated in vivo in a stroke model using PET imaging.

Methods: [^{18}F] DPA-714 was administered in a rat model of 2 hours transient middle cerebral artery occlusion (tMCAO) using 1, 4, 7, 11, 15, 21 and 30 days of reperfusion. We performed *in vitro* binding using autoradiography, and *in vivo* dynamic imaging using µPET, including displacement studies, and analyzed the stroke lesion with several markers using immunohistochemistry at different time points.

Results: *In vivo* PET imaging showed a significant increase at day 7, day 11, day 15 (P<0.01) and day 21 ($P<0.05$) in the stroke area with respect to the contralateral area. The highest binding value was reached at 11 days after ischemia relatively to 7 and 15 days (P<0.05). [^{18}F] DPA-714 uptake decreased at 21 days and 30 days with respect to uptake at 11 days (P<0.001).
In vitro binding using DPA-714 was performed at 1, 4, 7, 11 and 15 days after ischemia in order to confirm the results obtained in vivo with PET. An increase in binding was observed at 4 days (P<0.05), followed by a further increase from day 7 to day 15 (P<0.001). Binding was maximal at 11 days after ischemia in relation to day 4 (P<0.05) and day 7 (P<0.01) but not significantly higher than at day 15.
Displacement studies using *in vivo* PET imaging and *in vitro* binding with PK11195 and DPA-714 showed a rapid and complete displacement of [^{18}F] DPA-714 binding from the lesion.
The immunohistochemistry studies showed an increase of TSPO expression in amoeboid cells (monocytic lineage) in the core of infarction, and in astrocytes in the periphery of the infarcted area from days 7 to 15 after ischemia. At day 30, the presence of astrocytes increased in the core, thus indicating the presence of an astrocytic scar.

Conclusion: [^{18}F] DPA-714 appears as a good tracer for the study of the inflammatory reaction following stroke. This tracer will be further evaluated for its potential to document the effect of different anti-inflammatory strategies on TSPO expression.

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References
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