Evaluation of 18F-FA-4 and 11C-pipzA-4 as Radioligands for the In Vivo Evaluation of the High-Affinity Choline Uptake System

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Abstract

4,4′-Bis-1-hydroxy-2-(4-methylpiperidin-1-yl)ethyl-biphenyl (A-4), a tertiary amine analog of hemicholinium-3 (HC-3), is an inhibitor of the sodium-dependent high-affinity choline uptake (HACU) system. We have evaluated 4-[1-hydroxy-2-(4-^{18}F-fluoromethylpiperidin-1-yl)ethyl]-4′-[1-hydroxy-2-(4-methylpiperidin-1-yl)ethyl]biphenyl (^{18}F-FA-4) and 4-[1-hydroxy-2-(4-^{11}C-methylpiperazin-1-yl)ethyl]-4′-[1-hydroxy-2-(4-methylpiperidin-1-yl)ethyl]biphenyl (^{11}C-pipzA-4), an ^{18}F- and a ^{11}C-labeled derivative of A-4 as potential in vivo tracers for the HACU system. **Methods:** The biodistribution of both compounds was determined in mice, and the intracerebral distribution was visualized by ex vivo and in vitro autoradiography. The in vitro affinity of the compounds was determined by a displacement study with ^{3}H-HC-3 on mice brain slices. **Results:** In mice, both tracers show a high and persistent brain uptake. In vitro autoradiography shows binding to the striatum, whereas ex vivo autoradiography shows homogeneous binding throughout the brain. FA-4 and pipzA-4 inhibited the ^{3}H-HC-3 binding with a 50% inhibitory concentration of 57 nmol/L and 320 nmol/L, respectively. **Conclusion:** The evaluated compounds have affinity for HACU and show high uptake in the brain. In vitro binding of the compounds to the striatum cannot be inhibited by the presence of HC-3, whereas binding of HC-3 was inhibited by the presence of both FA-4 and pipzA-4, suggesting allosteric binding.