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Evaluation of iodinated and brominated [^{11}C]styrylxanthine derivatives as *in vivo* radioligands mapping adenosine A_{2A} receptor in the central nervous system

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In vivo assessment of the adenosine A_{2A} receptors localized in the striatum by PET or SPECT offers us a new diagnostic tool for neurological disorders. In the present study, we evaluated the potential of iodinated and brominated styrylxanthine derivatives labeled with ^{11}C as an *in vivo* probe. [7-Methyl-^{11}C]-(*E*)-3,7-dimethyl-8-(3-iodostyryl)-1-propargylxanthine ([^{11}C]IS-DMPX) and [7-methyl-^{11}C]-(*E*)-8-(3-bromostyryl)-3,7-dimethyl-1-propargylxanthine ([^{11}C]BS-DMPX) were prepared by the ^{11}C-methylation of corresponding 7-demethyl derivatives. An *in vitro* membrane binding study showed a high affinity (Ki values) of the two ligands for A_{2A} receptor: 8.9 nM for IS-DMPX and 7.7 nM for BS-DMPX, and a high A_{2A}/A_1 selectivity: >1100 for IS-DMPX and 300 for BS-DMPX. In mice, [^{11}C]IS-DMPX and [^{11}C]BS-DMPX were taken up slightly more in the striatum than in the reference regions such as the cortex and cerebellum. The uptake ratios of striatum to cortex and striatum to cerebellum gradually increased but were very small: 1.6–1.7 for the striatum-to-cortex ratio and 1.2 for the striatum-to-cerebellum ratio at 60 min postinjection. The uptake by these three regions was reduced by co-injection of an excess amount of carrier or an A_{2A} antagonist KF17837, but not by an A_1 antagonist KF15372. The blocking effects in the three regions were greater for [^{11}C]BS-DMPX (32–57%) than for [^{11}C]IS-DMPX (6–29%). *Ex vivo* autoradiography confirmed that the two ligands were slightly concentrated in the striatum. [^{11}C]BS-DMPX showed more selective affinity for adenosine A_{2A} receptors than [^{11}C]IS-DMPX, but these results have shown that the two tracers were not suitable as *in vivo* ligands because of low selectivity for the striatal A_{2A} receptors and a high nonspecific binding.

Key words: halogenated xanthine, adenosine A_{2A} receptor, PET, SPECT