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Short Research Article

Can 6-[^{18}F]fluoroDOPA be an accurate alternative for β-[^{11}C]DOPA?†

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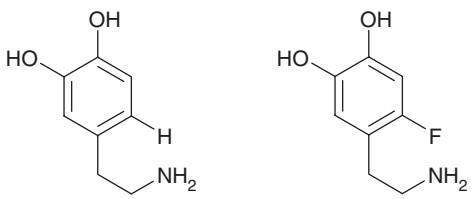
Introduction

The preparation of enantiomerically pure β-[^{11}C]DOPA as a routine tracer for visualization of dopamine metabolism in the brain is a continuous challenge for radiochemists. Both enzymatic and chemical multistep syntheses have been developed;[1–3] none of them is reliable enough for day-to-day production. [^{13}N]DOPA is not a practical option due to the short half-life of nitrogen-13 and its low specific activity.[4] 6-[^{18}F]fluoroDOPA, which is easier to prepare, is often used as an alternative to β-[^{11}C]DOPA. Considerable attention has been paid to disclose differences in pharmacokinetics of β-[^{11}C]DOPA and 6-[^{18}F]fluoroDOPA. Both transport to the brain and decarboxylation rates were studied in a number of publications.[5] One potential difference was omitted in these studies – the fluorine atom present in 6-[^{18}F]fluoroDOPA is potentially able to form a (strong) hydrogen bond with surrounding biologic structures including receptors and other parts of biomembranes thus resulting in different behaviour of 6-fluoroDOPA and 6-fluorodopamine compared to the non-fluorinated analogues.



dopamine 6-fluorodopamine

Results and discussion

Accurate quantum-chemical modelling of such interactions is not easy due to uncertainty of which biological structure to choose, their unknown *in vivo* conformations and high computational cost of calculation for large systems. Modelling of an intramolecular hydrogen bond between the fluorine atom of fluorodopamine and the hydrogen atoms of the amino group which mimics an amino group of a protein could be an attractive alternative. The small size of the system enables accurate geometry modelling at MP2 level with low computational cost. Indeed, geometry optimization of both dopamine and 6-fluorodopamine revealed significant differences in intramolecular interactions in vacuum. In dopamine, the only intramolecular hydrogen bond exists in –H…OH between two phenolic hydroxy groups. In 6-fluorodopamine there are two kinds of intramolecular hydrogen bonds H…OH and F…HN. On the maps of total electron density the F…HN bond is clearly seen as a bridge between the hydrogen atom and the fluorine atom. One should expect similar F…H interaction in real biological systems. *In vivo* the interactions could lead to differences in the biodistribution and metabolic rates of dopamine and 6-fluorodopamine. In some cases it may even be case that the behaviour of the two compounds could not be accurately described by using a similar compartmental model, even allowing for variations in the appropriate rate constants. This has been attempted in the past, however.[5] In such cases PET results obtained with 6-fluoroDOPA should not be considered as a correct approach to visualize dopamine distribution in the brain.

For the MP2 modelling of the geometries, the TZV(d) basis set was used in the quantum-chemical package

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PC GAMESS 7.0.[6] Rendering of the images was performed with MOLEKEL 4.3.[7] More accurate modelling is underway.

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