Abstract

The five subtypes of the dopamine receptor play an important role in the human brain. The dopamine D_4 receptor is involved in processes of behaviour control and is assumed to be responsible for the emergence of the attention deficit hyperactivity disorder (ADHD) as well as psychotic diseases like schizophrenia. While most of the other dopamine receptors are well known there is a lack of suitable radioligands for the examination of the D_4 receptor by functional neuroimaging via positron emission tomography (PET). This is due to the extremely low distribution density of D_4 in the central nervous system. In this work the radiosynthesis of such D_4 ligands was developed and pharmacologically evaluated. Therefore, selected pharmaceutical lead structures were labelled via nucleophilic substitution with no-carrier-added (n.c.a.) [^{18}F]fluoride at an aromatic ring and subsequently coupled in a 1-2 step build-up reaction to the desired ligands.

As first approach, an efficient radiosynthesis of the highly selective [^{18}F]FAUC 316 ligand ([^{18}F]**1**) was developed. Starting from ^{18}F-labelling of the symmetric iodonium salts bis(4-bromophenyl)iodonium triflate and bis(4-iodophenyl)iodonium triflate the corresponding 4-[^{18}F]fluorohalobenzenes were obtained in radiochemical yields (RCY) of up to 60 %. Pd-catalyzed cross-coupling of the labelling products and piperazine with $Pd_2(dba)_3$ or $Pd(OAc)_2$ led to 4-[^{18}F]fluorophenylpiperazine in a RCY of up to 42 %. During the synthesis of standard and precursors 5-Cyanoindol-2-carbaldehyd was synthesized in four reaction steps with an overall yield of 15 % and coupled to [^{18}F]FAUC 316. The overall-RCY after high performance liquid chromatography (HPLC) separation was 10 %.

[^{18}F]FAUC 316 was not suitable for further evaluation steps *in vivo* due to the very high non-specific binding content determined by *in vitro* autoradiography. Alternatively, the radioligands 6-(4-[4-[^{18}F]fluorobenzyl]piperazine-1-yl)benzodioxine ([^{18}F]**33a**), 6-(4-[4-[^{18}F]fluoro-(3-methoxy-benzyl)]piperazine-1-yl)benzodioxine ([^{18}F]**33b**), 6-(4-[4-[^{18}F]fluoro-(3-hydroxybenzyl)]piperazine-1-yl)benzodioxine ([^{18}F]**33d**) und 6-(4-[6-[^{18}F]fluoropyridine-3-yl]piperazine-1-yl)benzodioxine ([^{18}F]**33e**) were synthesized as benzodioxine derivatives with decreasing lipophilicity. For this 1-(1,4-benzodioxine-6-yl)piperazine (**30**) was coupled with the corresponding aldehyde derivatives by a reductive amination reaction in overall-RCY of 35 %, 20 %, 9 % and 15 %, respectively.

In vitro autoradiography on rat brain slices confirmed the correlation between non-specific binding and lipophilicity and lend [^{18}F]**33d** and [^{18}F]**33e** as putative radiotracers. Since [^{18}F]**33e** showed better D_4 selectivity, *ex vivo* organ uptake, metabolization rate and brain distribution were determined.

Examinations showed a principle qualification of [^{18}F]**33e** for the visualization of the D_4 receptors, but due to a lack of experiences a clear relation of D_4 to the ligand was not possible up to now. Further examinations *in vivo* are required to verify the ability of mapping D_4 receptors by this new radioligand.