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In vivo evaluation of [^{123}I]-3-(4-iodobenzyl)-1,2,3,4-tetrahydro-8-hydroxychromeno [3,4-*c*]pyridin-5-one: a presumed dopamine D_4 receptor ligand for SPECT studies

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Abstract

[^{123}I]-3-(4-iodobenzyl)-1,2,3,4-tetrahydro-8-hydroxychromeno[3,4-*c*]pyridin-5-one ([^{123}I]-ITCP), a presumed radioligand for visualization of the dopamine D_4 receptor by single photon emission computed tomography, was evaluated in vivo in mice and rabbits. This new radioiodinated tracer exhibited high brain uptake (3.64% injected dose per gram of tissue at 10 min p.i.) in mice. No significant amounts (less than 5%) of labeled metabolites were present in the brain, as demonstrated by a metabolite study. Regional brain distribution in rabbits showed atypical CNS uptake with consistently low values in the cortex and high values in other brain parts including cerebellum. Saturable binding was confirmed by a competition experiment with unlabeled product. Selectivity was assessed by competition experiments with a known dopamine D_4 ligand and later with a σ receptor ligand. Both experiments showed no observable competition. In conclusion, our findings indicate that [^{123}I]-ITCP is neither a dopamine D4 receptor ligand nor a σ receptor ligand. The exact nature of [^{123}I]-ITCP binding in the brain remains to be elucidated.

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1. Introduction

Schizophrenia is a severe form of mental illness affecting 7 per 1000 of the adult population, mostly aged 15–35 years. Although the incidence is low (3–10,000), the prevalence is high due to chronicity. Between 25% and 50% of schizophrenic patients attempt suicide, and 10% eventually succeed, contributing to a mortality rate eight times higher than in the general population. In the United States, over 20% of all social security benefits for daycare are used for the care of schizophrenic patients and the direct and indirect costs of schizophrenia are believed to be in the tens of billions of dollars annually [1].

The classical dopamine hypothesis of schizophrenia is based on the correlation between clinical doses of antipsychotic drugs, with prototype haloperidol, and their potency to block the dopamine D_2 receptor [2,3]. The dopamine receptors have been classified into five subtypes based on molecular biology data: the D_1-like receptors (D_1 and D_5) and the D_2-like receptors (D_2, D_3 and D_4). The D_4 receptor has recently received substantial attention, particularly since this receptor is thought to be the target for atypical (causing much less side effects) antipsychotic drugs, with prototype clozapine [4]. The interest in dopamine D_4 receptors and their role in schizophrenia was primarily sparked by two observations. The first one reported that the atypical antipsychotic clozapine has a 10-fold higher affinity for the dopamine D_4 receptor than for the dopamine D_2 receptor and that this affinity correlated well with its antipsychotic activity [4,5]. Furthermore, reports indicated that where

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classical neuroleptics need to occupy at least 70% of D_2 receptors to have antipsychotic effects (extrapyramidal symptoms occurring at 80% occupation), clozapine occupied only about 40% in therapeutical doses [6,7]. This suggested that the high efficacy and low prevalence of adverse effects of clozapine could be related to its affinity for the dopamine D_4 receptor. Secondly, it has been reported that there is a 6-fold increase in dopamine D_4 receptor density in the brain tissue of schizophrenic patients when compared to normal individuals, which also suggests an important role for the dopamine D_4 receptor in the pathophysiology of schizophrenia [8,9]. However, later observations could not confirm higher density of D_4 receptors in schizophrenics [10,11]. It also became clear that occupation of the D_2 receptor by clozapine was higher than initially thought (85%) [12]. It is now assumed that D_4 blockade by itself is not sufficient to alleviate positive symptomatology of schizophrenia and that D_2 receptor blockade is probably indispensable. However, D_4 receptor blockade is thought to be responsible for lower propensity of extrapyramidal side effects [5].

A limiting factor in the study of the dopamine D_4 receptor is the lack of specific radiotracers. At this point, the best known technique for in vivo visualization of the D_4 receptor subtracts the binding of nemonapride or spiperone and raclopride. The first molecules bind to all D_2-like receptors while raclopride only binds to D_2 and D_3 receptors. This system is far from ideal because nemonapride shows affinity for σ receptors while spiperone shows affinity for serotonin receptors. Moreover, there have been reports of a raclopride-insensitive dopamine D_2 receptor further complicating interpretation of the results of these experiments [5]. Thus, a selective tracer for the dopamine D_4 receptor could greatly facilitate research into the function of this receptor and its involvement in various disorders.

The original goal of this research project was to synthesize an [^{123}I]-labeled dopamine D_4 ligand for in vivo visualization of the dopamine D4 receptor using single photon emission computed tomography. The selection of anc 1[^{123}I]-3-(4-iodobenzyl)-1,2,3,4-tetrahydro-8-hydroxychromeno[3,4-*c*]pyridin-5-one ([^{123}I]-ITCP) (**1**) (Fig. 1) was based upon an article published by Unangst et al. [13]. They showed that anc 2 3-(4-chlorobenzyl)-1,2,3,4-tetrahydro-8-hydroxychromeno[3,4-*c*]pyridin-5-one (**2**) (Fig. 1) possesses high affinity for the dopamine D_4 receptor (pK_i=8.61) and shows more than 1000-fold selectivity over D_2 (pK_i=5.55) and more than 100-fold selectivity over D_3 (pK_i=6.50) receptors [13]. From these data it was assumed that the iodinated derivative would also show selectivity for the D_4 receptor. In addition, Unangst et al. [13] synthesized anc 3 3-(4-chlorobenzyl)-8-methoxy-1,2,3,4-tetrahydrochromeno[3,4-*c*]pyridin-5-one **3** (Fig. 1), which also showed good selectivity for the D_4 receptor (pK_i=8.06, <5.23 and 5.56 for D_4, D_2 and D_3 receptors, respectively). In 2002 however, Zhang et al. reported that 3-(4-chlorobenzyl)-8-[^{11}C]methoxy-1,2,3,4-tetrahydrochromeno[3,4-*c*]pyridin-5-one was not a dopamine D_4 antagonist but a potential tracer for σ_1 receptors (IC_{50}=105 nm). This was tested by in vitro autoradiography of rat brain sections and in vivo PET studies with rhesus monkeys [14].

Given the fact that affinities for both D_4 and σ_1 receptors are in the same order of magnitude it indeed seems likely that these ligands would behave as σ receptor ligands in vivo rather than as D_4 ligands. This is due to the fact that the density of D_4 receptors (<30 fmol/mg protein) in the brain is much lower than that of σ_1 receptors (400–600 fmol/mg protein) [15–17]. Since binding in vivo is governed by the B_{max}/K_d ratio it is clear that σ receptor binding is more likely to occur. In this work, both D_4 and σ binding were investigated.

2. Materials and methods

2.1. Chemicals and radiochemicals

All chemical reagents were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used without further purification. Solvents were purchased from Lab-Scan analytical sciences (Dublin, Ireland). [^{123}I] Sodium iodide (in 0.05 M NaOH) was purchased from Bristol-Myers Squibb Pharma (Brussels, Belgium). L-745-870 and BD 1008 were purchased from Tocris Cookson (Bristol, UK).

2.2. Chemistry

Synthesis and radiosynthesis of [^{123}I]-ITCP was performed as previously described [18]. Radiochemical yield was 68±3% (n=5), with a radiochemical purity of >95% and a specific activity of >2.96 Ci/μmol.

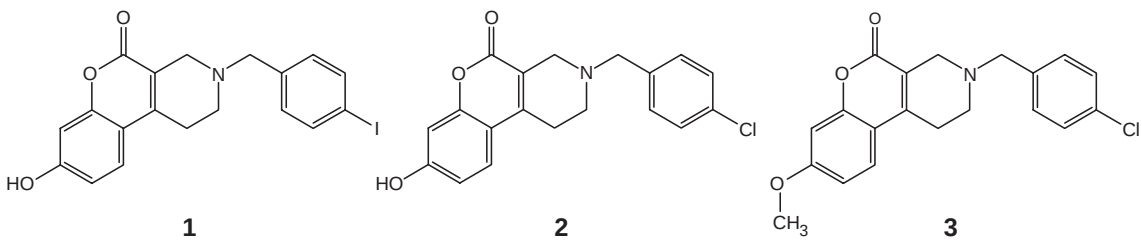

Fig. 1. Structures of anc 1[^{123}I]-ITCP (**1**), anc 2 3-(4-chlorobenzyl)-1,2,3,4-tetrahydro-8-hydroxychromeno[3,4-*c*]pyridin-5-one (**2**) and anc 3 3-(4-chlorobenzyl)-8-[^{11}C]methoxy-1,2,3,4-tetrahydrochromeno[3,4-*c*]pyridin-5-one (**3**).

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