Effects of single and repeated administration of 1,2,3,4-tetrahydroisoquinoline analogs on the binding of [11C]raclopride to dopamine D₂ receptors in the mouse brain

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Summary. We investigated the effects of intraperitoneal injection of 1,2,3,4-tetrahydroisoquinoline (TIQ) analogs and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) on the binding of [11C]raclopride to striatal dopamine D₂ receptors in mice. The binding of [11C]raclopride, but not of [11C]N-methylspiperone or [11C]nemonapride with higher affinity, to the receptors was significantly decreased immediately after TIQ injection. Neither a dopamine transporter blocker induced such effect nor TIQ affected the dopamine transporter-radioligand binding. Among the compounds investigated, including parkinsonism-inducing TIQ and (R/S)-1-benzyl-TIQ, parkinsonism-preventing (R)- and (S)-1-methyl-TIQ, and probable N-methylated metabolites of TIQ and 1-methyl-TIQ, TIQ and (S)-1-methyl-TIQ had the strongest effect on the binding of [11C]raclopride, and N-methylated derivatives showed less of an effect than the respective parent compounds. The decrease in the binding of [11C]raclopride continued for 7 hours and was followed by an increase until 10 days after the single and subchronic administration of TIQ. These findings suggest that TIQ analogs profoundly stimulated dopamine release which resulted in the competitive inhibition of the binding of [11C]raclopride to dopamine D₂ receptors, but did not induce degeneration of the receptors.

Keywords: 1,2,3,4-tetrahydroisoquinoline, dopamine release, raclopride, Parkinson’s disease.

Introduction

Parkinson’s disease is characterized by the degeneration of nigrostriatal dopaminergic neurons, but the pathogenesis of the disease remains unknown, despite extensive study using animal models. 1,2,3,4-Tetrahydroisoquinolines
(TIQs) are endogenous substances that have specific neurotoxic effects on the dopaminergic system producing parkinsonism in experimental animals (Dostert et al., 1988; Nagatsu, 1997; Nagatsu and Yoshida, 1988) as does 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Collins and Neafsey, 1985; Gerlach et al., 1996). In contrast, another endogenous TIQ analog, 1-methyl-1,2,3,4-tetrahydroisoquinoline (1-MeTIQ) (Kohno et al., 1986; Makino et al., 1990; Niwa et al., 1987; Ohta et al., 1987), is considered a possible parkinsonism-preventing compound. The bradykinesia, a symptom of parkinsonism, induced by MPTP, TIQ or (R/S)-1-benzyl-1,2,3,4-tetrahydroisoquinoline (1-BnTIQ) was completely prevented by pretreatment with 1-MeTIQ in mice (Tasaki et al., 1991; Kotake et al., 1995).

Both MPTP and TIQ induced parkinsonism; however, some differences between the two animal models are reported. The loss of tyrosine hydroxylase-positive cells in the substantia nigra was confirmed following treatment with MPTP and TIQ (Ferger et al., 1999; Lorenz-Koci et al., 2000; Ogawa et al., 1989), but Ogawa et al. (1989) did not find TIQ-induced neuronal loss in the substantia nigra by Cresyl Violet staining. In the case of 1-BnTIQ, Abe et al. (2001) found that 1-BnTIQ did not induce the loss of tyrosine hydroxylase-positive cells in spite of the bradykinesia-inducing effect. Recently we found that TIQ and 1-BnTIQ did not reduce the in vivo specific binding of two radiolabeled ligands, N-3-fluoropropyl-2-β-[O-methyl-11C]carbomethoxy-3-β-(4-iodophenyl)-tropane ([11C]CIP-FP) and 2-β-carbomethoxy-3-β-(4-fluorophenyl)-[N-methyl-11C]tropane ([11C]CFT, [11C]WIN 35,428), to presynaptic dopamine transporters on the mouse striatum (unpublished data), suggesting no degeneration of nigrostriatal dopaminergic neurons. On the other hand, we found that the in vivo specific binding of [3H]raclopride to the postsynaptic dopamine D_2 receptors was temporarily reduced 3 days, but not 10 days, after the 4-day TIQ treatment. The temporal reduction probably reflects the competitive inhibition of the [3H]raclopride-dopamine D_2 receptors binding with synaptic dopamine, not degeneration of postsynaptic dopamine D_2 receptors. It is well known that the in vivo binding of raclopride is greatly influenced by the concentration of endogenous dopamine (Dewey et al., 1993; Hartvig et al., 1997; Seeman et al., 1989), but it is not known whether TIQ analogs induce degeneration of postsynaptic dopamine D_2 receptors. Furthermore, a profound stimulation of dopamine release by TIQ, salsolinol and their derivatives was reported (Booth et al., 1989; Lorenz-Koci et al., 2000; Maruyama et al., 1992, 1993; Melchior et al., 1978). However, it is unknown whether other TIQ analogs such as 1-BnTIQ and 1-MeTIQ also have such an effect and how long the effect of TIQ on the stimulation of dopamine release remains after the treatment.

In the present study we investigated in vivo whether TIQ analogs and MPTP decrease the binding of radiolabeled raclopride to the striatal dopamine D_2 receptors in mice by competing with synaptic dopamine, compared with the binding of higher affinity radioligands: N-methylspiperone and nemonapride. The TIQ analogs investigated were TIQ, 1-BnTIQ, (R)- and (S)-1-MeTIQ, 2-methyl-1,2,3,4-tetrahydroisoquinoline (2-MeTIQ) and (R)-