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Molecular basis of the selective binding of MDMA enantiomers to the alpha4beta2 nicotinic receptor subtype: Synthesis, pharmacological evaluation and mechanistic studies

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ABSTRACT

The α4β2 nicotinic acetylcholine receptor (nAChR) is a molecular target of 3,4-methylenedioxymethamphetamine (MDMA), a synthetic drug also known as ecstasy, and it modulates the MDMA-mediated reinforcing properties. However, the enantioselective preference of the α4β2 nAChR subtype still remains unknown. Since the two enantiomers exhibit different pharmacological profiles and stereoselective metabolism, the aim of this study is to assess a possible difference in the interaction of the MDMA enantiomers with this nAChR subtype. To this end, we report a novel simple, yet highly efficient enantioselective synthesis of the MDMA enantiomers, in which the key step is the diastereoselective reduction of imides derived from optically pure *tert*-butylsulfinamide. The enantioselective binding to the receptor is examined using [^{3}H]epibatidine in a radioligand assay. Even though the two enantiomers induced a concentration-dependent binding displacement, (*S*)-MDMA has an inhibition constant 13-fold higher than (*R*)-MDMA, which shows a Hill's coefficient not significantly different from unity, implying a competitive interaction. Furthermore, when NGF-differentiated PC12 cells were pretreated with the compounds, a significant increase in binding of [^{3}H]epibatidine was found for (*R*)-MDMA, indicating up-regulation of heteromeric nAChR in the cell surface. Finally, docking and molecular dynamics studies have been used to identify the binding mode of the two enantiomers, which provides a structural basis to justify the differences in affinity from the differential interactions played by the substituents at the stereogenic centre of MDMA. The results provide a basis to explore the distinct psychostimulant profiles of the MDMA enantiomers mediated by the α4β2 nAChR subtype.

1. Introduction

3,4-Methylenedioxymethamphetamine (MDMA; Scheme 1), also known as ecstasy, is a synthetic drug widely abused in the United States and Europe, where it is taken in a recreational context due to its stimulant and hallucinogenic properties. Amphetamines produce a dose-dependent increase of locomotor activity in rodents [1], which reflects an increase of dopamine (DA) transmission in the nucleus accumbens [2]. Activation of nicotinic acetylcholine receptors (nAChRs) is a common event in the pathway used by several addictive drugs to stimulate the mesolimbic DA system, which is a relevant component of the brain stimulation reward pathway [3,4]. Thus, in rats systemic nicotine or alcohol administration elevates extracellular DA levels in the nucleus accumbens, an effect that requires stimulation of nAChRs in this area as well as in the ventral tegmental one, in which the mesolimbic dopaminergic cell bodies are located [5–7].

Abbreviations: AP, alternative pose; BP, best pose; CNS, central nervous system; DA, dopamine; MD, molecular dynamics; MDMA, N-3,4-methylenedioxymethamphetamine; nAChR, nicotinic acetylcholine receptor; QM/MM, quantum mechanical/molecular mechanical; SIE, Solvated interaction energy.

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