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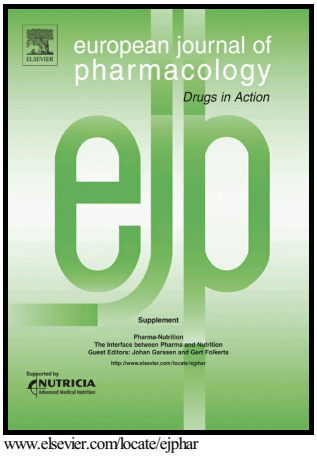

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Multiscale simulation of monoamine oxidase catalyzed decomposition of phenylethylamine analogs

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Abstract
Phenylethylamine (PEA) is an endogenous amphetamine and its levels are increased by physical activity. As with other biogenic monoamines, it is decomposed by monoamine oxidase (MAO) enzymes. The chemical mechanism of MAO, and flavoenzymes in general, is a subject of heated debate. We have previously shown that the rate-limiting step of MAO catalysis involves a hydride transfer from the substrate methylene group vicinal to the amino group to the N5 atom of the lumiflavin co-factor moiety. By using multiscale simulation on the Empirical Valence Bond (EVB) level, we studied the chemical reactivity of the monoamine oxidase B catalyzed decomposition of PEA and its two derivatives: *p*-chloro-β-methylphenylamine (*p*-CMP) and *p*-methoxy-β-methylphenethylamine (*p*-MMP). We calculated activation free energies of 17.1 kcal/mol (PEA), 18.4 kcal/mol (*p*-MMP) and 20.0 kcal/mol (*p*-CMP), which are in excellent agreement with the experimental values of 16.7 kcal/mol for PEA and 18.3 kcal/mol for *p*-MMP, while the experimental value for *p*-CMP is not available. This gives strong support to the validity of our hydride transfer mechanism for both MAO A and B isoforms. The results are discussed in the context of the interplay between MAO point mutations and neuropsychiatric disorders.

Keywords
monoamine oxidase; molecular simulation; QM/MM methodology; Empirical Valence Bond; neurotransmitters; phenylethylamine

1. Introduction

Monoamine oxidases (MAOs) are enzymes found on the mitochondrial membrane of cells (Edmondson et al., 2009; Youdim et al., 2006). The reaction they catalyze is the oxidative deamination of biogenic and dietary monoamines (Abad et al., 2013; Poberžnik et al., in print; Repič et al., 2014b; Vianello et al., 2012; Zapata-Torres et al., 2015) such as dopamine, serotonin, histamine, noradrenaline and phenylethylamine. MAOs exist in two isoforms, MAO A which mainly decomposes serotonin and MAO B which predominantly metabolizes dopamine and phenylethylamine (Shih et al., 1999). The human A and B isoforms are quite similar, sharing 70% of amino-acid sequence and the same lumiflavin cofactor (Bach et al., 1988). By calculating the pK_a values of ionizable residues and comparing the corresponding active site geometries, we have shown that MAO A and MAO B have very similar preorganized electrostatics and that it is very likely that both isoforms catalyze reactions by the same chemical mechanism (Repič et al., 2014a), although this has been questioned in the literature (Orru et al., 2013).