Antipsychotic clozapine binding to alpha-2-macroglobulin protects interacting partners against oxidation and preserves the anti-proteinase activity of the protein

Abstract

In this study, the interaction between clozapine, an atypical antipsychotic drug, and alpha-2-macroglobulin (α_2M), a multipurpose anti-proteinase, was investigated under simulated (patho) physiological conditions using multiple spectroscopic techniques and molecular modeling. It was found that α_2M binds clozapine with a moderate affinity (the binding constant of 0.9×10^5 M^{-1} at 37 °C). The preferable binding site for both clozapine's atropisomers was revealed to be a large pocket at the interface of C and D monomer subunits of the protein. Hydrogen bonds and the hydrophobic effect were proposed as dominant forces in complex formation. The binding of clozapine did not induce significant conformational change of the protein, as confirmed by virtually unaltered α_2M secondary structure and anti-proteinase activity. However, both clozapine and α_2M shielded each other from the deleterious influence of strong oxidants: sodium hypochlorite and 2,2′-azobis-2-methyl-propanimidamide dihydrochloride (AAPH). Moreover, clozapine in a concentration range that is usually targeted in the plasma during patients' treatment effectively protected the anti-proteinase activity of α_2M under AAPH-induced free radical overproduction. Our results suggest that the cooperation between α_2M and clozapine may be a path by which these two molecules synergistically protect neural tissue against injury caused by disturbed proteostasis or oxidative stress.