Mapping of the Allosteric Site in Cholesterol Hydroxylase CYP46A1 for Efavirenz, a Drug That Stimulates Enzyme Activity*

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Abstract

Cytochrome P450 46A1 (CYP46A1) is a microsomal enzyme and cholesterol 24-hydroxylase that controls cholesterol elimination from the brain. This P450 is also a potential target for Alzheimer disease because it can be activated pharmacologically by some marketed drugs, as exemplified by efavirenz, the anti-HIV medication. Previously, we suggested that pharmaceuticals activate CYP46A1 allosterically through binding to a site on the cytosolic protein surface, which is different from the enzyme active site facing the membrane. Here we identified this allosteric site for efavirenz on CYP46A1 by using a combination of hydrogen-deuterium exchange coupled to MS, computational modeling, site-directed mutagenesis, and analysis of the CYP46A1 crystal structure. We also mapped the binding region for the CYP46A1 redox partner oxidoreductase and found that the allosteric and redox partner binding sites share a common border. On the basis of the data obtained, we propose the mechanism of CYP46A1 allostery and the pathway for the signal transmission from the P450 allosteric site to the active site.

- allosteric regulation
- Alzheimer disease
- brain

- cholesterol
- cholesterol metabolism
- cytochrome P450
- drug design
- hydrogen-deuterium exchange

Footnotes

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