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Study of structural-chemistry of sodium 4-phenylbutyrate on its binding to serum albumin

Masaki Otagiri and **Keishi Yamasaki**
Sojo University, Japan

Sodium 4-phenylbutyrate (PB) is phenyl-substituted fatty acid derivative that is clinically used for the treatment of urea cycle disorders by its ammonium scavenging activity. PB has also other pharmacological activities such as an inhibitor of endoplasmic reticulum stress and histone deacetylases. However, the binding of PB to plasma protein is not fully understood. Thus, we investigate the binding of PB to plasma protein in detail. Binding experiments showed that PB mainly binds to human serum albumin (HSA) with a single high affinity site, site 2. Moreover, the hydrophobic and electrostatic interactions play an important role on the binding based on structure-activity relationship and thermodynamic analysis. In addition, Tyr411 and Arg410 were involved in the binding of PB to site 2, from the binding experiments using chemically modified HSAs and mutant HSAs. These findings were confirmed by X-ray crystallographic analysis: the carboxylate group of PB hydrogen-bonded to Arg410, Tyr411 and Ser489, and the alkyl chain, including the phenyl group of PB, occupies the hydrophobic cavity of drug site 2. Next, we examined binding properties of PB to mammalian serum albumin. PB was also found to interact with one high affinity site, which corresponds to site 2 of HSA and several number of low affinity binding sites in all albumins. The affinities of PB to human and bovine albumins were higher than those to rabbit and rat albumin, and that to rabbit was the lowest. Binding and molecular docking studies using structurally related compounds of PB suggested that species differences in the affinity are attributed to differences in the structural feature of PB-binding sites on albumins (e.g. charge distribution, hydrophobicity, shape, or size). The findings presented herewith will be useful for understanding the pharmacokinetics and the pharmacological effects of PB.

Recent Publications

1. Kawai A, Chuang V T G, Kouno K, Yamasaki K, Miyamoto S, et al. (2017) Crystallographic analysis of the ternary complex of octanoate and N-acetyl-L-methionine with human serum abumin reveals the mode of their stabilizing interactions. Biochim Biophys Acta 1865:979–984.
2. Yamasaki K, Kawai A, Otagiri M, et al. (2017) Species differences in the binding of sodium 4-phenylbutyrate to serum albumin. J Pharm Sci 106:2860–2867.
3. Enokida T, Yamasaki K, Otagiri M, et al. (2016) Tyrosine 411 and arginine 410 of human serum albumin play an important role in the binding of sodium 4-phnybutyrate to site II. J Pharm Sci 105:1987–1994.
4. Yamasaki K, Chuang V T G, Maruyama T and Otagiri M (2013) Albumin-drug interaction and clinical implication. Biochim Biophys Acta 1830:5435–5443.

Biography

Masaki Otagiri is currently a Professor and Dean of Faculty of Pharmaceutical Sciences, Sojo University. He graduated from Nagoya City University with a PhD Degree in 1975. In 1980, he joined the Pharmaceutics Department of Faculty of Pharmaceutical Sciences, Kumamoto University as an Associate Professor and then promoted to Professor of Biopharmaceutics Department, Kumamoto University in 1983. After his retirement from Kumamoto University in 2009, he was appointed as Professor of Faculty of Pharmaceutical Sciences, Sojo University, Kumamoto, Japan.

otagirim@ph.sojo-u.ac.jp

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