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Brain Protective Drug Nimodipine Influences the Metabolic Elimination of Irinotecan

Zheng-Rong LI *

The Second Affiliated Hospital of Xingtai Medical College, Xingtai, 054000, Hebei, China

***SUMMARY*. Nimodipine is an important drug clinically used to treat subarachnoid hemorrhage, and this study aims to evaluate drug-drug interaction between nimodipine and irinotecan which a first-line anti-tumor drug. Due to the importance of UDP-glucuronosyltransferase (UGT) 1A1 towards the metabolism of irinotecan, homology modeling was employed to get the crystal structure of UGT1A1, and the chemical structure of nimodipine was docked into the crystal structure of UGT1A1 using AutoDock software. Nimodipine can be well docked into the activity cavity of UGT1A1, and the amino acids residues in the activity cavity contain Gly-12, Ser-13, His-14, Gly-34, Asp-37, Gln-82, Arg-83, Thr-87, Lys-90, Phe-128, His-148, Ala-149, Leu-150, Gly-263, Leu-282, Ser-284, Met-285, Gln-332, His-347, Ala-348, His-351, Gly-352, Phe-369, Gly-370, Gln-372, and Asn-375. Further analysis showed that hydrogen bonds and hydrophobic interactions contributed the strong interaction between nimodipine and the activity cavity of UGT1A1. Nimodipine formed three hydrogen bonds with amino acids residues Ser-13, Ser-284, Met-285, and Ser-350. Nimodipine generated hydrophobic interaction with amino acids Gly-12, His-14, His-35, Arg-83, Lys-90, Phe-128, His-148, Ala-149, Gly-283, Ser-284, Gly-349, Phe-369, Asp-371, and Gln-372. In conclusion, this study indicated the importance for monitoring clinical nimodipine-irinotecan interaction.**

RESUMEN. La nimodipina es un fármaco importante clínicamente utilizado para tratar la hemorragia subaracnoidea, y este estudio tiene como objetivo evaluar la interacción fármaco-fármaco entre nimodipina e irinotecan que un fármaco antitumoral de primera línea. Debido a la importancia de la UDP-glucuronosiltransferasa (UGT)1A1 para el metabolismo del irinotecán, se empleó un modelo de homología para obtener la estructura cristalina de UGT1A1 y la estructura química de nimodipina se acopló a la estructura cristalina de UGT1A1 utilizando el software AutoDock. La nimodipina puede estar bien acoplada a la cavidad de actividad de UGT1A1, y los residuos de aminoácidos en la cavidad activa contienen Gly-12, Ser-13, His-14, Gly-34, Asp-37, Gln-82, Arg-83, Thr-87, Lys-90, Phe-128, His-148, Ala-149, Leu-150, Gly-263, Leu-282, Ser-284, Met-285, Gln-332, His-347, 348, His-351, Gly-352, Phe-369, Gly-370, Gln-372 y Asn-375. Un análisis posterior demostró que los enlaces de hidrógeno y las interacciones hidrofóbicas contribuyeron a la fuerte interacción entre nimodipina y la cavidad activa de UGT1A1. La nimodipina formó tres enlaces de hidrógeno con los residuos de los aminoácidos Ser-13, Ser-284, Met-285 y Ser-350. Nimodipina generó interacción hidrófoba con los aminoácidos Gly-12, His-14, His-35, Arg-83, Lys-90, Phe-128, His-148, Ala-149, Gly-283, Ser-284, Gly-349, Phe-369, Asp-371, y Gln-372. En conclusión, este estudio indicó la importancia de la monitorización clínica de la interacción nimodipina-irinotecan.

KEY WORDS: cerebral hemorrhage, drug-drug interaction, *in silico* docking, nimodipine, irinotecan, UDP-glucuronosyltransferase (UGT) 1A1.

* Author to whom correspondence should be addressed. *E-mail:* lizhengronghebei@126.com

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