Molecular dynamics simulations reveal how Sugammadex reverses muscle relaxants and interacts with anaesthetic agents

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Introduction: Sugammadex reverses neuromuscular blockade by rocuronium via a supramolecular mechanism of action. During the design process cyclodextrin host molecules were systematically modified to achieve the highest affinity between the cyclodextrin molecules and rocuronium therefore creating the most stable complex. Through these experiments the size of the hydrophobic binding cavity, electrostatic interactions and Van der Waals forces were found to be important determinants of structure-activity relationships. This was consistent with what is known about cyclodextrin chemistry from previous work (Adam et al., 2002). Our aim for this study was to create a computer model which would allow the dynamic interaction over time of the host and guest molecules to be dynamically visualised in real time and validate this computer simulation by comparison with experimental lab data and previously published data of affinity between various drugs and sugammadex (Zwiers et al., 2011).

Methods: Molecular dynamics (MD) simulations have been performed to understand the interaction of Sugammadex with selected Neuromuscular blocking agents (NMBAs), corticosteroids, anaesthetics and antibacterials using Gromacs2019. Drug molecules were docked into the sugammadex using AutoDock Vina as an initial step for the MD simulations. Change in enthalpy (ΔH) of encapsulated drugs within sugammedex were calculated using Poisson Boltzmann relation via gmx_MMPBSA package. We have verified our simulations with some cortical slice experiments monitoring the change in field potential neuronal population activity.

Results: The affinity of sugammadex with rocuronium and the other drugs modelled by computer simulation correlated with the experimental data previously published. This was measured by the change in enthalpy (ΔH) of the host-guest complex. It was our expectation that the negatively charged side chains would be the first point of binding between the molecules. This was not the case as the rocuronium was first encapsulated by the hydrophobic cavity and then held in place by the negatively charged side chains providing a very stable state. In an interesting finding, the computer simulated model showed some low affinity binding with propofol. This was then verified experimentally by showing that the effects of propofol on in vitro cortical slice model were attenuated by the addition of sugammadex.

Conclusion: Correlation of molecular interactions seen using the computer simulations and data from laboratory experiments as well as previously published data allows validation of the computer simulation model. This has provided some unexpected results around real time molecular interactions between sugammadex and rocuronium and propofol.

Adam, Julia M., et al. "Cyclodextrin-Derived Host Molecules as Reversal Agents for the Neuromuscular Blocker Rocuronium Bromide: Synthesis and Structure− Activity Relationships. " Journal of Medicinal Chemistry 45.9 (2002): 1806-1816.

Zwiers, Alex, et al. "Assessment of the potential for displacement interactions with sugammadex. " Clinical drug investigation 31.2 (2011): 101-111.

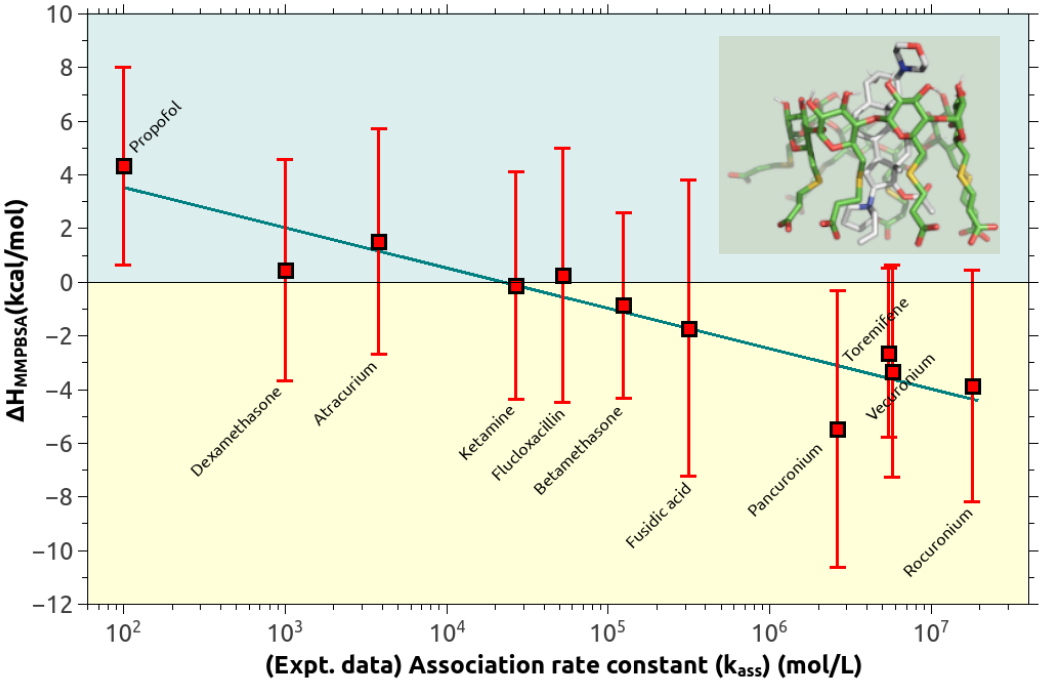

Figure 1. Correlation between change in enthalpy (ΔH) from computational simulations and the experimental data taken from *Zwiers et al., 2011.* The inset shows how sugammadex encapsulates rocuronium.