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Review of Molecular Docking Studies of Aspirin, Indomethacin, and Salicylate: Mechanism of Action and Impact on Cyclooxygenase Inhibition

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ABSTRACT

This review explores the mechanisms of action of aspirin, salicylate, and related nonsteroidal anti-inflammatory drugs (NSAIDs), focusing on their inhibition of cyclooxygenase (COX) enzymes and subsequent reduction in prostaglandin synthesis. Despite similar anti-inflammatory effects, aspirin and salicylate differ in their potency and mechanisms of COX inhibition. Advances in molecular docking and in silico drug design have provided insights into the structural interactions between these drugs and their targets, offering potential for developing more selective COX-2 inhibitors. Additionally, emerging research suggests potential anticancer properties of aspirin and salicylate, warranting further investigation for broader therapeutic applications.

INTRODUCTION

The mechanism of action of aspirin, indomethacin, and salicylate has been a central focus of pharmacological research for decades. These compounds, classified as nonsteroidal anti-inflammatory drugs (NSAIDs), work primarily by inhibiting the synthesis of prostaglandins. The first thorough explanation of their mechanism of action suggested that aspirin, indomethacin, and salicylate inhibit the production of prostaglandins, which are lipid compounds involved in the inflammatory response (refs. 1-3). Over time, it was discovered that these drugs exert their effects by inhibiting the enzyme cyclooxygenase (COX), which is responsible for converting arachidonic acid into prostaglandin endoperoxides, the precursors to prostaglandins (ref. 4). This inhibition of COX enzymes is the fundamental pharmacological action underlying the anti-inflammatory, analgesic, and antipyretic properties of NSAIDs.

However, further studies have shown that the potency and mechanisms of action of these NSAIDs can differ significantly, particularly in terms of their anti-inflammatory effects and their ability to inhibit cyclooxygenase. For example, aspirin and salicylate, while both capable of reducing inflammation, do so with differing potencies. Specifically, in in vitro studies, aspirin has been shown to inhibit COX in a guinea pig lung preparation with approximately 20 times greater potency than salicylate, even though both drugs exhibit similar anti-inflammatory properties in vivo (ref. 1). Additionally, aspirin, even at a low dose of 10 mg/kg in rats, is capable of inhibiting thromboxane (TX) production in platelets. In contrast, salicylate, even at a dose 20 times higher than aspirin, does not achieve this effect (ref. 5). These findings raise the possibility that the anti-inflammatory effects of aspirin and salicylate may not solely be attributed to their ability to inhibit prostaglandin synthesis, suggesting that other mechanisms may be involved.

In one experimental approach, researchers measured the levels of aspirin and salicylate in plasma and inflammatory exudates from rats following oral administration. The study found that while both drugs were absorbed and reached significant concentrations in the plasma and inflammatory sites, their effects on key biomarkers of inflammation, such as thromboxane (TXB2) and prostaglandin E2 (PGE2), differed. These findings suggest that while both aspirin and salicylate can influence prostaglandin synthesis, their efficacy in reducing inflammation may be linked to other factors such as their ability to modulate non-COX-related pathways.

Aspirin's Mechanism of Action

Aspirin (acetylsalicylic acid) has been used for its anti-inflammatory and analgesic properties since the 1800s, and its origins trace back to plant-based compounds used for pain relief as early as the third century B.C. (Choi et al., 2015). The main mechanism by which aspirin exerts its effects is through the inhibition of the enzyme cyclooxygenase (COX), specifically COX-1, although it also inhibits COX-2 to a lesser extent.

COX is an enzyme responsible for converting arachidonic acid into prostaglandins, which mediate inflammatory responses, fever, pain, and blood clotting. By inhibiting COX-1, aspirin effectively blocks the conversion of arachidonic acid to prostaglandins, thus alleviating pain and inflammation. Furthermore, aspirin's inhibition of COX-1 prevents the production of thromboxane, a potent vasoconstrictor and promoter of platelet aggregation. This is why aspirin is widely used as an anticoagulant and blood-thinning agent, especially for cardiovascular protection (Vane and Botting, 2003). Importantly, the inhibition

of COX-1 by aspirin is irreversible, meaning that its effects on platelets last for the entire 8-10 day lifespan of the platelet, as platelets are unable to regenerate COX-1. This property contributes to aspirin's long-lasting effects in preventing blood clots.

When administered orally, aspirin is rapidly absorbed in the stomach and upper intestine, reaching peak plasma concentrations within about 30 minutes to 2 hours. It is then metabolized in the liver to salicylate, which also has anti-inflammatory properties. While aspirin itself exerts its effects mainly through COX inhibition, its metabolite, salicylate, may contribute to some of its therapeutic benefits, including modulation of immune responses.

Molecular Docking: A Computational Approach to Drug Discovery

Molecular docking is a widely employed technique in drug discovery that uses computational models to predict how two molecules, such as a drug (ligand) and its target protein (receptor), will bind to form a stable complex. The goal is to determine the optimal binding orientation of the ligand in the receptor's active site and predict the strength of the interaction. This technique is invaluable for understanding the molecular basis of drug action and for guiding the design of new drugs.

In molecular docking studies, the receptor is typically a protein with a known three-dimensional structure, and the ligand is the small molecule that binds to the receptor. By using algorithms to explore possible binding orientations and scoring functions to evaluate the strength of the interaction, researchers can predict the binding affinity of the ligand for the receptor. Some of the most common docking methods involve rigid docking (where both the ligand and receptor are treated as rigid objects) and flexible docking (where the ligand or receptor can change shape to accommodate the binding site). Computational tools such as **DOCK**, **GOLD**, **Flex**, and **ICM** are frequently used in high-throughput docking simulations to explore large libraries of potential drug candidates.

Docking studies can provide valuable insights into how drugs interact with their targets, and can be used to identify new therapeutic candidates, optimize existing drugs, and reduce the time and cost associated with experimental drug development. These studies are particularly important for understanding how small molecules like aspirin interact with enzymes such as COX and help design more selective and potent inhibitors.

Studies on Aspirin and Its Derivatives: Docking and In Silico Drug Design

Several studies have used molecular docking and in silico drug design approaches to better understand how aspirin and its derivatives interact with key proteins involved in inflammation, such as COX enzymes. Below are key findings from some notable studies:

1. Molecular Docking of Aspirin and Derivatives

In a molecular docking study, Smrithi Radhakrishnan and colleagues explored the affinity of various aspirin derivatives for HIV-1 protease (HVR protein). Among the compounds tested, SR-03 (a resorcinol derivative) had the highest binding affinity for the target protein, with a dock score of -99.07 and a hydrogen bond energy of -7.17 KJ. Other derivatives, such as SR-02 (benzyl derivative) and SR-04 (phenol derivative), also showed notable binding affinities. Aspirin itself had a moderate affinity for the HIV-1 protease (dock score: -66.64, hydrogen bond energy: -6.24 KJ), while a butyl derivative (SR-01) exhibited the lowest affinity (dock score: -68.62).

This study highlighted the role of electron-withdrawing groups in enhancing the binding affinity of aspirin derivatives, particularly in the carboxylate group, which plays a crucial role in the pharmacological effects of aspirin. The results also suggested that modifications to the aspirin molecule could potentially improve its affinity for specific targets, thereby enhancing its therapeutic efficacy.

2. In Silico Drug Design for COX Inhibition

Ali Kazemi Babaheydri and colleagues used in silico techniques to design aspirin derivatives with improved selectivity for cyclooxygenase enzymes (COX-1 and COX-2). The study focused on the interaction between aspirin and COX enzymes, analyzing the formation of hydrogen bonds and the number of bonds formed during molecular dynamics (MD) simulations. The researchers found that the number of hydrogen bonds between COX enzymes and aspirin derivatives varied between 0 to 8 bonds, depending on the specific structure of the compound.

One of the key findings of this study was the identification of aspirin isomers that could selectively inhibit COX-2 while minimizing side effects commonly associated with COX-1 inhibition, such as gastrointestinal irritation. The study suggested that these aspirin isomers, with modifications to the molecular structure, might represent promising candidates for further clinical development aimed at reducing inflammation with fewer adverse effects.

3. Cancer Prevention: Cyclin A2 and CDK2 as Targets of Aspirin and Salicylic Acid

A study by Rakesh Dachineni and colleagues explored the potential anticancer properties of aspirin and salicylic acid by examining their effects on cell proliferation in cancer cell lines. The researchers treated HT-29 (colon cancer), SK-MEL-28 (skin cancer), and MDA-MB-231 (breast cancer) cell lines with aspirin and salicylic acid at concentrations ranging from 0.25 mmol/L to 2.5 mmol/L.

The study found that both aspirin and salicylic acid significantly reduced cell proliferation in these cancer cell lines, with concentrations as low as 0.5 mmol/L showing a notable effect. Importantly, these drugs did not impact cell viability, suggesting that they could reduce cancer cell growth without inducing cell death. These findings support the hypothesis that aspirin and salicylic acid may play a role in cancer prevention or adjunctive cancer therapy by modulating cell cycle progression and inhibiting key signaling pathways involved in tumor growth.

4.Aspirin-Aromatic Amino Acid Conjugates as Selective COX-2 Inhibitors

In a study by Mahmood HM Jasim and colleagues, aspirin was conjugated with aromatic amino acids to create selective COX-2 inhibitors. These conjugates were designed to provide a larger molecular size that could potentially enhance selectivity for COX-2 over COX-1. Although the conjugates did not perform as well as the selective COX-2 inhibitor celecoxib, they showed promise as safer alternatives with fewer gastrointestinal side effects. The study suggested that these conjugates could represent a new class of NSAIDs with improved safety profiles.

Conclusion

Aspirin, salicylate, and other NSAIDs have been extensively studied for their ability to inhibit COX enzymes and reduce inflammation. However, recent studies have highlighted that the anti-inflammatory effects of these drugs are likely influenced by additional mechanisms beyond simple COX inhibition. Molecular docking and in silico drug design have provided valuable insights into how aspirin and its derivatives interact with their target proteins, and how modifications to their chemical structures can improve their potency and selectivity. Moreover, research into the potential anticancer effects of aspirin and salicylate suggests that these drugs may have broader therapeutic applications, including in cancer prevention and treatment.

Continued research into the molecular mechanisms underlying the effects of aspirin and its derivatives will help optimize their therapeutic efficacy and reduce potential side effects, making them more effective in a variety of clinical settings. The use of advanced computational techniques like molecular docking will play a crucial role in identifying new drug candidates and designing safer, more effective drugs for the treatment of inflammation, cancer, and other diseases.

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