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PROMISCUITY OF NSAIDS, THE SECRET OF THEIR EFFECTIVENESS: PERSPECTIVE

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Abstract

Analgesics, especially NSAIDs including acetaminophen as an analgesic, are drugs with small structures; this article reviewed DrugBank, Pubmed and Chembl and compared descriptors like lipinsky rule and QED for NSAIDs, including acetaminophen, and states that Promiscuity as an advantageous property has not been considered for this group of drugs, but its large number of known receptors and their size, prove that this term fits perfectly.

Keywords: Nsaids; promiscuity; COX 1; COX 2, Lipinsky rules

Introduction

Analgesics are drugs designed to ameliorate pain and are classified in groups, including opiates, corticosteroids, analgesics adjuvants (e.g. antidepressants), and nonsteroidal anti-inflammatories, NSAIDs, presenting their particularities especially in their mechanisms of action, nature and therapeutic applications. Due to the similarities in the method of action, analgesics are clustered in many groups, including nonsteroidal anti-inflammatory drugs, NSAIDs, and analgesics derived from p-aminophenol, though their anti-inflammatory action is limited. The NSAIDs structures share their analgesic method of action while having distinctive structures. Their structures are also similar as they present a small molecular weight and physicochemical parameters that confirm their availability through oral administration. Analgesics described in the study have been related to the nonsteroidal anti-inflammatories, sharing their analgesic effects. Although their molecular structures share some similarities, they are in fact quite different however, one of their most highlighted feature is their small molecular size.

Methods

This paper evaluated and compared lipinsky rules and Quantitative estimate druglikeness QED for NSAIDs including acetaminophen, as well as the number of receptors included in databases DrugBank CHEMBL and PUBCHEM. It includes a review on promiscuity as an advantage in small molecules and recent advances in mechanisms of action known for NSAIDs and acetaminophen.

Results and Discussion

Analgesics described in this essay show a close but complex, not well defined relationship in terms of structure-activity. In the case of acetaminophen, at least three different analgesic methods of action are known. The polypharmacology is an application in the rational design of drugs and a significant advantage for patients' positive outcomes, the analgesics described in the essay share specially this feature over many others. Just in the case of Dipyrone, a drug that has called the attention of many researchers, 116 prospective receptors have been described.

According to this commentary, just NSAIDs represent about 70 million of prescriptions in the US and 30 million are sold every year. [1] Given the high rates of consumption, the understanding of NSAIDs should get special attention. The European Molecular Biology and Cheminformatics Laboratory Database (CHEMBL), the Drug Bank, PubChem, and others have reported the most recent information in terms of analgesic drugs and many other therapeutic molecules in different developmental stages. Some of the most important properties of medical chemistry are summarized in table 1. Taking acetylsalicylic acid as the base for salicylates, acetaminophen for para-aminophenol's and dipyrone for the pyrazolone-derived compounds.

Every property or descriptor used in medical chemistry reflects its optimal value in each case. In the three examples of table 1, it is possible to observe acceptable liposolubility (logP<5); polar surface which predicts the required size to get in to the cell (<140Å), as well as the values of the Lipinski rule.[2,3] It is important to highlight there is no molecule that does not fulfill the Lipinski rule.

QED (Quantitative Estimation of Drug-affinity) has been estimated in molecule banks as it is a good statistical descriptor in drug design. QED values predict the feasibility of the medication for oral administration (0.2-0.8).[4]

According to this commentary, the promiscuity of a molecule is the key to understand the effectiveness of these drugs. These structures possess the ability to join an important number of described receptors, and there are many more studies in computational chemistry and *in vitro* that reports the affinity of these molecules to the corresponding receptors.

The promiscuity of a molecule may be explained, in part, by the dosage or concentration of the drug during its time in the body as the number of the receptors is fundamental to promiscuity to take part. Mencher and colleagues (10) found that aspirin and salicylate at their therapeutic concentration might inhibit the expression of the COX-2 transcript. On the other hand, higher pharmacological concentration may inhibit NFκB transcription, protecting tissues from injury. Similarly, another study performed by Szegezdi and colleagues (11) explains how the concentration of the drug may influence the promiscuity of itself by affecting the expression of receptors and transcripts, for example, 2.5 up to 5.0mM of aspirin induce the transcription of DcR1 and DcR2 receptors in colo205 cells.

Regarding the mechanisms shared by the analgesics described in the current essay, it is important to highlight the results reported by Flower in the Nature magazine in 1972, stating the inhibition of prostaglandin synthesis by the action of NSAIDs.[5] For many scientist, these findings are in fact, a jewel of scientific literature in terms of painkillers, a work that has been cited more than 500 times and it is up to date, an important reference in elucidating new mechanisms for new and existing painkillers.

Thanks to the work of Flower, Nakano[6] , and other related researchers, it is possible to understand in part, the main method of action for NSAIDs. The main receptors of NSAIDs are the enzymes prostaglandin H2 synthase-1, also called cyclooxygenase-1 (COX-1), and prostaglandin H2 synthase-2, also called cyclooxygenase-2 (COX-2). Structural differences in both enzymes are few; one of the differences is on the COX-2 active site, which is 20% larger than in COX-1, due to a substitution of an isoleucine instead of a valine at position 523. Additionally, there are differences in other aminoacids, one of the most interesting change is in the case of Serine-530 in COX-1 and Serine-516 in COX-2, both are responsible for irreversible binding of aspirin. [7,8]

Nowadays, there is an important tendency to infer about the promiscuity of existing drugs and even to take into account the promiscuity as an important feature in drugs design; this is not just to increase its therapeutic possibilities but also to understand the pharmacokinetics of new prospective drugs. A promiscuous drug has the advantage that it is metabolized in more than one region of the cytochrome p450, or to achieve its effectiveness by more than just one mechanism, as with the case of acetaminophen.

Recently, a proliferation of research in computational chemistry, in vitro and in vivo trials has been observed, seeking new therapeutic opportunities based on the chemical structure of existing drugs. The judgment of a selective drug, summarized in the phrase "one target-one drug" has been refuted with evidence that proves that the activity can be benefited by the promiscuity of the drug.

Despite the tendency of drugs of being useful in more than one pharmacological domain, promiscuous properties in analgesics have been described long time ago, as an example, just in the case of acetylsalicylic acid, 169 receptors or targets have been described. In 1989, when inhibition of cyclooxygenase 1 and 2 was the main mechanism of action, Abramson and Wissman proposed simultaneous mechanisms in inflammation mediation, including neutrophil blocking in the cell membrane. [9] Therefore, we can now attribute the success of the analgesics described in this essay to their promiscuity feature, contrary to COX-2 that does not present this feature.

While the terms polypharmacology and promiscuity do not pretend to describe analgesics, but rather to be a beneficial observation of other chemical groups, the medicinal chemistry evidenced in this essay demonstrate how these terms fit perfectly to analgesics, especially in the case of Acetaminophen.

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Table 1. Descriptors of small structure analgesics.

Molecule	ALogP	Polar surface area Å,	hydrogen acceptor	Hydrogen donor	Rotatable Bonds	Molecular weight g/mol	QED	receptors reported	references
acetylsalicylic acid	1	63,6	4	1	3	180,15	0,56	169	CHEMBL 461522 PubChem Compound Database; CID=3111
Acetaminophen	0,71	49,33	2	2	1	151,16	0,58	151	CHEMBL112 PubChem Compound Database; CID=1983
Dipyrone	0,38	89,54	6	1	4	311,36	0,81	116	CHEMBL25 PubChem Compound Database; CID=2244