

Non-Steroidal Anti-Inflammatory Drugs (Nsaids) Rapidly Alter Heart Rate In Invertebrate Model

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are most commonly used drugs worldwide. Most NSAIDs block the production of prostaglandins through inhibiting cyclooxygenases (COXs) thus causing anti-pyretic, analgesic, and anti-inflammatory effects. Although, effects and some side-effect of these drugs are known, their effects on the heart rate are not known.

We tested the effects of common NSAIDs on the heart beats of *Daphnia*, an invertebrate model organism. We observed that aspirin, ibuprofen and naproxen increased the heart rate rapidly. On the other hand, nimesulide caused instant decrease in the heart rate. It is a recent trend to use NSAIDs especially aspirin for controlling heart diseases, therefore, it is very important to evaluate these drugs for their effects on the heart rate. The data reported here suggests that there is an urgent need to evaluate the effects of these drugs on human heart.

Introduction

More than 50 NSAIDs are available worldwide that include some of the routinely prescribed drugs. Major NSAIDs may be salicylates (e.g. aspirin), arylalkanoic acids (e.g. diclofenac), profens (e.g. ibuprofen, naproxen), sulfonanilides (nimesulide) and oxicams (e.g. piroxicam) [1]. Although, NSAIDs differ in structure and properties, but mostly they block the production of prostaglandins by inhibiting cellular cyclooxygenases (COXs) that results into anti-pyretic, analgesic, and anti-inflammatory effects of these molecules [2]. Prostaglandins are important mediators of cellular inflammation in most tissues. Therefore, NSAIDs are specially prescribed for inflammatory diseases. However, the

mode of COX inhibition differ between aspirin and non-aspirin NSAIDs, as, unlike non-aspirin NSAIDs, aspirin blocks COX by stable acetylation [3]. Main side-effect of these drugs include blood-thinning or anticoagulative effect, reduced prostaglandin-dependent defense, hampered mucosal blood flow etc. Interestingly, aspirin has also been useful in controlling severity of various types of cardiovascular ailments to an extent that it has been reported to minimize death in many such cases [4].

Daphnia are also known as “water fleas”, and commonly found in ponds and lakes [5]. *Daphnia* has been an important model for research, as it has comparatively short life cycle, and can easily be maintained [6]. These organisms can feed on microscopic organisms including phytoplanktons [6]. *Daphnia* have transparent body that facilitates observation of internal organs including heart [7]. These organisms are covered by a thin membrane, therefore, compounds dissolved in water can easily enter inside the body of these organisms [5]. The heart rate of *Daphnia* can be monitored by using a compound microscope having real-time imaging capability [8].

Daphnia's life span is in between 35-60 days, which varies with the environmental conditions. Male and female *Daphnia* can be identified by the presence/absence of brood pouch, which is present in females only. Eggs that are present in brood can develop into embryos and subsequently new individuals.

Materials and Methods

***Daphnia* Culture**

Daphnia were grown in 300 ml containers having filtered river water or aged tap water with yeast culture (0.5%), added after 3rd day. Yeast cells can be used as food for *Daphnia* [9]. Cultures were monitored regularly.

Heart-rate Counting

In a given population, individual *Daphnia* can have significantly different heart rate. Therefore, to find the effect of selected compounds, live viewing of the heart rate of individual *Daphnia* is needed. We used a microscope that had real-time imaging capability, and, for each *Daphnia*, Control heart-beat was counted first. Afterwards, alterations in the heart rate was recorded after adding drugs. *Daphnias* were placed on a slide having 100 microlitre of water. The slide was viewed in microscope.

Results and Discussion:

Effects of NSAIDs on the heart-beat have not been investigated. We recorded the effect of most common NSAIDs on the heart-beat. We observed that aspirin, ibuprofen and naproxen increased the heart rate rapidly. On the other hand, nimesulide caused instant decrease in the heart rate (Figure 1). Nimesulide, a COX-2 selective NSAID, caused 9.58% (mean value) reduction in the heart-beat. Aspirin caused 9.91% (mean value) increase, ibuprofen caused 8.45% (mean value) increase, and naproxen also caused 10.74% (mean value) increase. It is commonly believed that most NSAIDs have similar effects. We, however, observed that their effect is very different on heart rate. Interestingly, we also compared the different effects of these NSAIDs in combination of

dopamine, which is a major neurotransmitter. Different NSAIDs synergized in different manner with dopamine (Figure 2). Dopamine caused reduction in the heart rate in combination of either ibuprofen or aspirin, but increased the heart rate in combination of naproxen (Figure 2). Moreover, dopamine caused further reduction of nimesulide-induced heart rate (Figure 2).

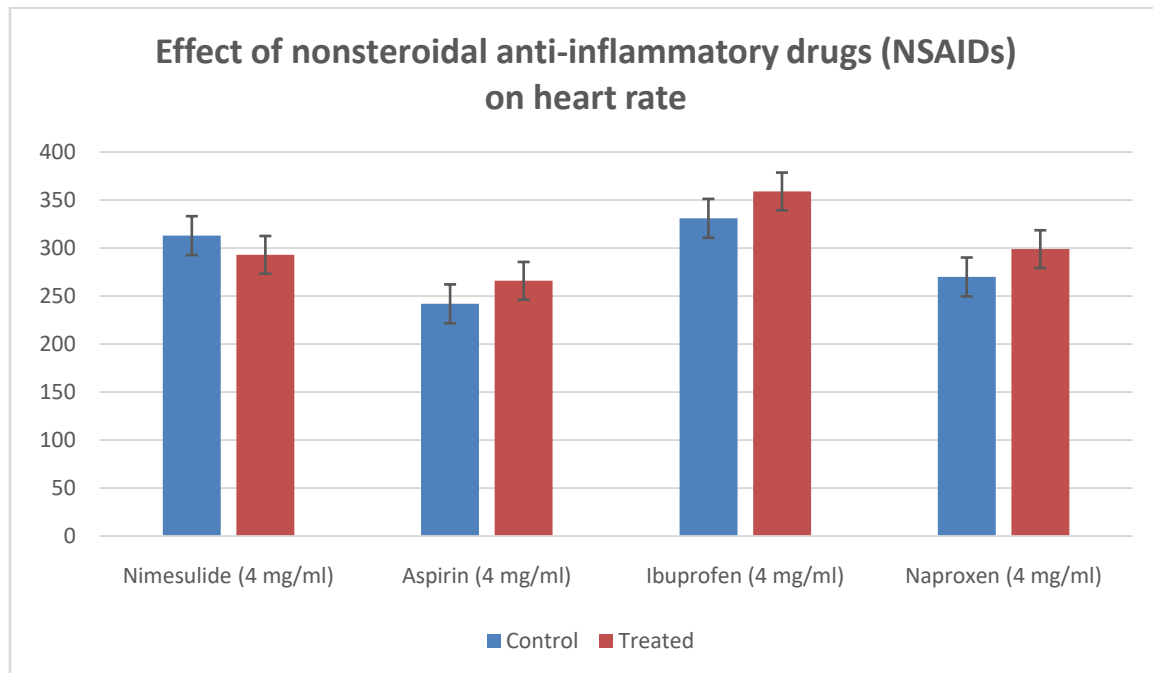


Fig. 1. NSAID's effect on the heart rate of *Daphnia*.

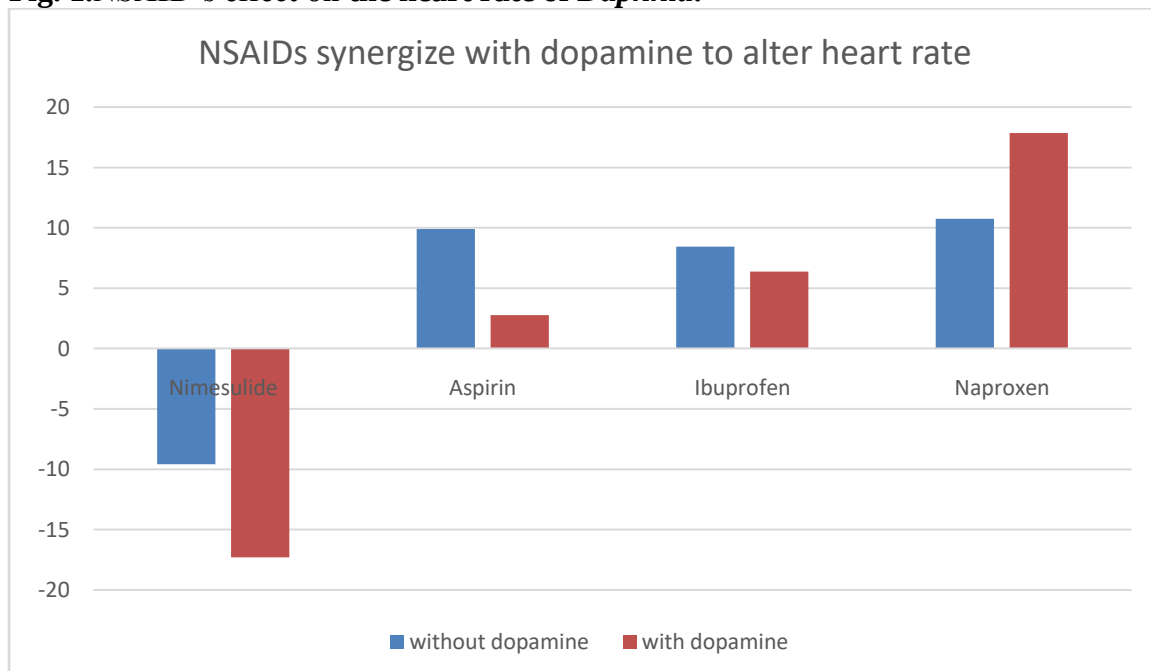


Fig. 1. NSAIDs synergize with dopamine to change the heart rate of *Daphnia*.

Conclusion:

This study can be of much use, as NSAIDs are common drugs, and, dopamine is the key neuromolecule [10]. Despite common use of these drugs, their effect on the heart rate was recently recognized [11]. NSAIDs effect on the heart rate of invertebrate model necessitates the evaluation of such effects of these agents in mammals. As, cardiac disorders are the leading causes of mortality in current times, this investigation can be of paramount importance. If similar effects of these agents are observed in humans, several treatment and preventive protocols of cardiac ailments should be modified in light of this study, for e.g.a heart patient should only be prescribed NSAIDs, if the respective cardiomodulatory effect(s) of these agents are known.

Author Contributions

AK did all the experimental work and data compilation. GS prepared the paper.

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