

INVESTIGATION OF NEW NSAIDS FOR THE TREATMENT OF INFLAMMATORY DISEASES OF KIDNEY AND URINARY TRACT

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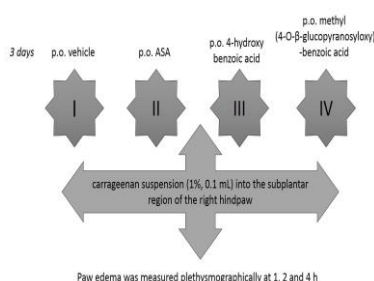
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Graphical abstract



Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the world, primarily due to their high efficiency for the treatment of inflammatory induced pain syndrome. The main feature of NSAIDs is a combination of anti-inflammatory, analgesic, antipyretic, and anticoagulant properties. However, their long-term use is associated with side effects in the gastrointestinal tract including peptic ulcers and other. We developed and synthesized molecule of methyl (4-O- β -glucopyranosyloxy)-benzoic acid. The anti-inflammatory effect of methyl (4-O- β -glucopyranosyloxy)-benzoic acid evaluated using the carrageenan-induced hindpaw edema model. The study shows that the intragastrically administration of test substance to animals reduces inflammatory process.

Keywords: Pain, analgesic, phenolic glycosides, writhing test

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1.0 INTRODUCTION

NSAIDs are non-steroidal anti-inflammatory drugs, also known as NAIDs, non-steroidal anti-inflammatory agents/analgesics (NSAIDs) or non-steroidal anti-inflammatory medicines (NSAIDs). NSAIDs are the leaders of the consumption in the world. They are used for prevention and treatment of inflammatory diseases, arthritis, pain, fever, and ischemic cerebrovascular disorders because of their anti-inflammatory, analgesic, antipyretic, and anti-platelet functions. The uniqueness of NSAIDs as a class of drugs has been referred to the combination of anti-inflammatory, analgesic, antipyretic, and anticoagulant properties [1]. The pathogenesis of the vast majority of diseases associated with inflammation results in pain syndrome that impairs the quality of

patient's life. NSAIDs are among the most commonly used drugs worldwide, and are taken by more than 30 million people every day, and 40% patients older than 60 years. About 20% of hospitalized patients receive NSAIDs in base treatment. The analgesic activity of NSAIDs used not only in acute inflammatory diseases, but it use for cancer prevention and therapy with weakly and moderately pain syndrome [2]. Reduced platelet aggregating capacity for patients at high risk of heart attack and stroke significantly extends life span. However, we must remember that there are a number of individuals with thrombocytopenia and new anti-inflammatory drugs does not affect the present hemostasis in great request now [3]. Despite the high effectiveness of this group of agents necessary to consider pronounced side effects. Long-term use of NSAIDs carries a lot of complications. The

most common side effects are disorders of the digestive tract mucosa [4]. In addition to upper gastrointestinal complications, such as gastric and duodenal ulcers, complications in the small intestine and colon can occur, which cause bleeding, perforation, stricture, and chronic problems, such as iron deficiency anemia and protein loss [5]. Increased blood pressure caused by the inhibition of cyclooxygenase kidney consequence sodium and water retention in the body with a prevalent by cardiovascular system[6]. There are complications such as leukopenia and agranulocytosis, thrombocytopenia in the hematopoietic system [7, 8]. A serious side effect is toxic to hepatocytes caused by damage to the mitochondria, which are no longer adequately provide the energy-intensive processes [9]. In connection with the above we are developing NSAID with a pronounced therapeutic effect and, if possible, no side effects.

In this study, we investigated methyl 4-(β -D-glucopyranosyloxy) benzoate has anti-inflammatory activity for carrageenan-induced hind paw edema model and compared this with activity of references drugs. Therefore, methyl 4-(β -D-glucopyranosyloxy) benzoate was obtained follow glycosylation method of methylparaben with boron trifluoride and then deprotected by sodium methylate [10]. The structure and purity of all acetylated products were proven by complex of analysis (mp, IR, NMR and GH/MS).

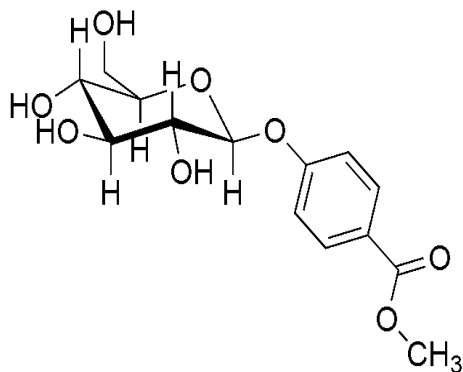


Figure 1 Chemical structure of methyl 4-(β -D-glucopyranosyloxy) benzoate

2.0 MATERIALS AND METHODS

2.1 Drugs and Pharmacological Treatments

The following drugs were used: acetylsalicylic acid (ASA) (Irbit's chemical-pharmaceutical factory, Russia), metazolol sodium (Moscow Pharmaceutical Factory, Russia).

2.2 Chemistry

Melting points, which are uncorrected, were determined using MP50 Melting point system (Mettler toledo). IR spectra were recorded with IR Fourier

spectrophotometer Spectrum BX II using KBr disks. The ^1H and ^{13}C NMR spectra were recorded on Bruker-300 MMX spectrometer at 300 and 75.5 MHz, respectively, in DMSO-d_6 and $\text{D}_2\text{O-d}_2$ with TMS as an internal standard. The chemical shifts are given in δ (parts per million) and the spin-spin coupling constants (J) in hertz. GC-MS analysis was performed using Agilent 7890A/5975C GC/MSD instrument follow [11].

2.3 Animals

Male Wistar rats (200–250 g) were obtained from the Institute of Cytology and Genetics SB BAS, Novosibirsk, Russia. All animals were housed at constant room temperature and humidity under a 12 h light/dark cycle (lights on at 7 AM) with food and water ad libitum. All experimental procedures were performed in accordance with «European Convention for the Protection of Vertebrate Animals used for experimental and other scientific purposes» Strasbourg, (1986).

2.4 Assessment of Carrageenan-induced Inflammatory Response in the Rat Hindpaw

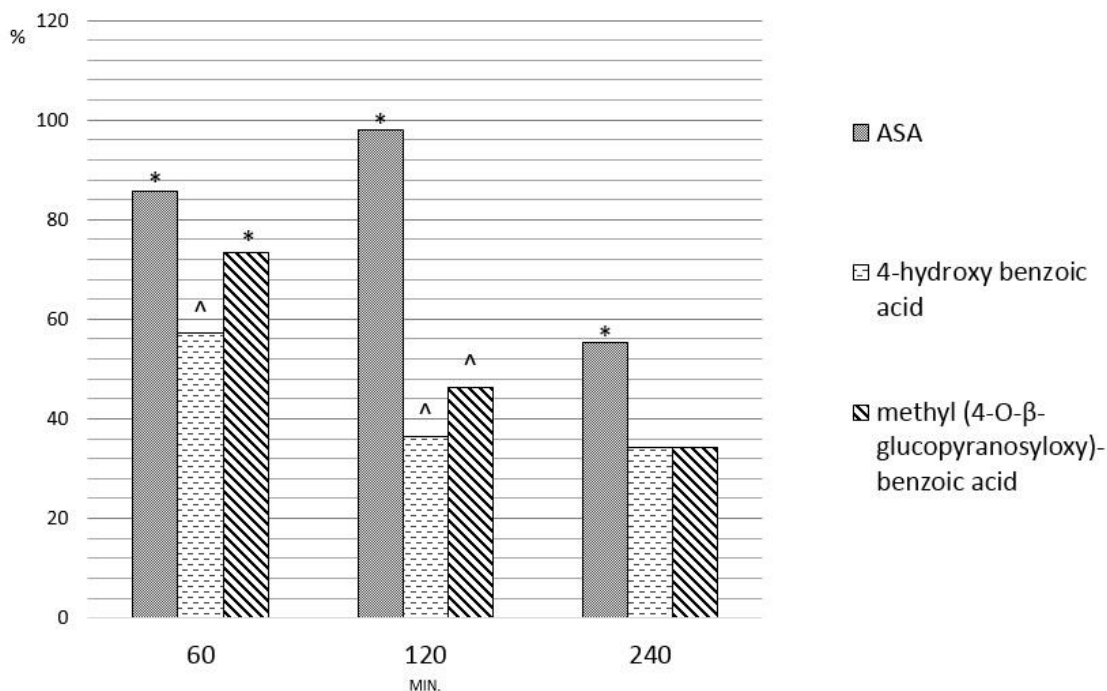
The anti-inflammatory effect of methyl (4-O- β -glucopyranosyloxy)-benzoic acid was measured using the carrageenan-induced hindpaw edema model [12, 13]. Briefly, carrageenan suspension (1%, 0.1 mL) was administered into the subplantar region of the right hindpaw of rats, previously treated (3 days and 60 min before, $n=10/\text{group}$) with methyl(4-O- β -glucopyranosyloxy)-benzoic acid (17 mg/kg, p.o.), acetylsalicylic acid (ASA) (20 mg/kg, p.o.), 4-hydroxy benzoic acid (17 mg/kg, p.o.), or vehicle (2 ml, purified water). Paw edema was measured plethysmographically at 1, 2 and 4 h after the carrageenan. The data obtained were expressed in mL. The percentage of inhibition was calculated by the formula:

$$X = (V_k - V_o) / V_k * 100 \quad (1)$$

V_k – the average gain of limbs in the control, sm^3 ;
 V_o – the average gain of limbs in the experiment, sm^3 .

2.5 Statistical analysis

For in vivo studies, the results were expressed as mean \pm standard error means (S.E.M.). Statistical evaluation of the data was performed using one-way analysis of variance (ANOVA) followed by Bonferroni's test. Values of $P < 0.05$ were considered statistically significant. graph in Figure 2 shows the anti-inflammatory activity study of the methyl (4-o- β -glucopyranosyloxy)-benzoic acid using carrageenan induced rat paw edema method.



*p < 0.01 as compared with control group, ^Δ p < 0.01 as compared with ASA group.

Figure 2 Anti-inflammatory activity study of the methyl (4-O-β-glucopyranosyloxy)-benzoic acid using carrageenan induced rat paw edema method

3.0 RESULTS

Administration of carrageenan solution to control animals led to rapid and consecutive formation of inflammatory edema in the experiment. In the early stages (60 min), the maximum effect of edema formation inhibition of inflammation was observed in rats under the effect of acetylsalicylic acid - 85,7% (P < 0,01). The maximum effect of acetylsalicylic acid observed after 120 min administration of carrageenan solution (98%, P < 0,01), but after 4 hours the effect decreased to 55% (P < 0,01). Figure 1 shows that the anti-inflammatory effect of methyl (4-O-β-glucopyranosyloxy) -benzoic acid reached statistical significance in 1 hour after injection of carrageenan, the volume reducing limb 73,8% (P < 0,01) compared with control group treated with vehicle. Values between group with oral administration ASA and group received the test substances in the first hour was not statistically different. However, the anti-inflammatory activity of methyl (4-O-β-glucopyranosyloxy) -benzoic acid was gradually reduce to the end of the experiment. Oral administration of 4 - hydroxybenzoic acid gave the maximal effect in the first hour from the start of administration of carrageenan, and then decrease in activity was observed to the end of the experiment. Antiphlogistic activity of the substance is 3 times lower than that of ASA (P < 0,05)

4.0 DISCUSSION

Carrageenan-induced inflammation is commonly used model for assessing the anti-inflammatory potency of compounds or natural products [14]. Schematically, we can distinguish several phases in the development of acute aseptic inflammation caused by carrageenan. The mechanism of action of carrageenan-induced inflammation: the first phase (10-20 min) is characterized by the release of histamine and serotonin, which activate kallikrein-kinin system in the accumulation kinins in the first hour. Kinins contribute to local release of hydrolytic lysosomal enzymes which stimulate the formation of prostaglandins. Prostaglandins are mediators the late phase of inflammation that develops in the carrageenan edema in 3 hours. The maximum of concentration of prostaglandin E2 in blood recorded after 12-24 hours. Further in this chain of events implicated the complement system, which operates in conjunction with kinin system and the blood coagulation. Several authors mention that the final phrase often combined into one, and carrageenan edema is seen as bi-phase process, the second stage which is the result of release of prostaglandins, lysosomal proteases and bradykinin [15]. The study shows that the intragastric administration to animals of methyl (4-O-β-glucopyranosyloxy) -benzoic acid affect the intensity and dynamics of the inflammatory process, as the result higher than the desired parameters anti-inflammatory activity (anti-inflammatory activity is 30%

suppression of edema). If we compare the obtained data with the results of the group received ASA, we can see that after 120 and 240 minutes after simulation of inflammatory response, anti-inflammatory activity of the methyl (4-O- β -glucopyranosyloxy) -benzoic acid was significantly lower compare with acetylsalicylic acid. In the first hour after administration of these drugs, their anti-inflammatory activity was not statistically different. From all the above we can assume that methyl (4-O- β -glucopyranosyloxy) -benzoic acid possible anti-inflammatory effect by inhibiting the synthesis of histamine, serotonin and kinins in the first hour.

5.0 CONCLUSION

This study shows that the methyl (4-O- β -glucopyranosyloxy) -benzoic acid has anti-inflammatory effect in the model of acute inflammation. However, to assess anti-inflammatory properties of a model is insufficient and requires additional experiments. Further study of this compound can help in the understanding of chemistry and molecular mechanisms of action of phenolic glycosides.

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