KHARKIV NATIONAL MEDICAL UNIVERSITY

BIOMEDICAL SCIENCES

Gaichuk Alesya, Darshan Divesh, Saveliev V.V.

EXPERIMENTAL STUDY OF THE INFLUENCE OF CELECOXIB, CAFFEINE AND THEIR PHARMACEUTICAL COMPOSITION ON THE LEVEL OF CERULOPLASMIN IN THE RATS' BLOOD SERUM UNDER THE CONDITIONS OF FORMALINE EDEMA

Department of Medical and Bioorganic Chemistry
Kharkiv National Medical University
Kharkiv, Ukraine
Scientific advisor: Pharm.D., professor Anna O.Syrovaya

It is presently known that inflammation development entails synthesis of a number of proteins, the so-called positive proteins of the acute phase of inflammation. Therefore, studying molecular mechanisms of interaction between the inflammatory process participants can be useful for development of diagnostic methods to define the inflammatory process severity, assessment methods to prove adequacy of the anti-inflammatory pharmacotherapy used, and also methods for creating new anti-inflammatory drugs.

It is known from the literature that one of the key proteins of the acute phase of inflammation is ceruloplasmin (CP, ferro:O2-oxidoreductase). Its concentration during inflammation reaches 10 μM, which is comparable to increase of such proteins as fibrinogen and haptoglobin in concentration during the acute phase of inflammation. CP has been studied in Europe for over 40 years. However, so far, no clear ideas about the pathophysiological role of this copper-containing ferroxidase have been formed. The record shows that CP has pronounced oxidase activity; in plasma, it also limits release of iron stores, activates oxidation of ascorbic acid, noradrenaline, serotonin and sulfhydryl compounds, and also inactivates reactive oxygen species, preventing lipid peroxidation. All this, in our opinion, explains expediency of studying CP content in blood during the acute phase of inflammation.

The problem of inflammation is faced by every doctor in his or her clinical practice. In order to effectively help the patient get rid of the pain accompanying inflammation and speed up recovery, it is necessary to understand the mechanisms of the inflammatory process development.

Materials and methods. To study the anti-inflammatory effect in laboratory animals (white rats, WAG line), biochemical studies were carried out with the purpose of

comparing the anti-inflammatory effect of celecoxib, caffeine and their pharmaceutical composition against the reference drug – diclofenac sodium.

The anti-inflammatory effect of the above substances was studied using an experimental model of formalin edema (f.e.). The rats were divided into 6 groups, 6 animals in each group. The animals of the 1st group were kept under control; they got one administration of 3% starch mucus (2 mL per 200 g of a rat) orally intragastrically (i.g.). For the animals of the 2nd group, f.e. was simulated through subplantar administration of 2% formalin solution into the hind paw of a rat, and i.g. administration of 3% starch mucus. The animals of the 3rd - 6th groups were administered once i.g. with the study drugs in form of 3% starch mucus suspension: the rats of the 3rd group – 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-pyrazole-1-yl]benzenesulfonamide (celecoxib) at the dose of 1.5 mg per 1 kg of animal body weight; the rats of the 4th group – 1,3,7-trimethylxanthine (caffeine) at the dose of 0.6 mg per 1 kg of animal body weight; the rats of the 5th group – pharmaceutical composition of celecoxib with caffeine in similar doses; the rats of the 6th group – diclofenac sodium (8 mg per 1 kg of animal body weight) as the reference drug. It is known that the maximum development of f.e. is observed 4 hours after its simulation. 3% starch mucus, the study drugs were administered 1 hour before this moment, considering their pharmacokinetic and pharmacodynamic features. The animals of all groups were decapitated under ether anesthesia.

The level of CP was determined using the Ravin test kit "Determination of ceruloplasmin in blood serum" (PrJSC "Reagent").

The results were statistically processed using the Statistics 6.0 software package. Reliability of the results obtained was established using the Student's t-test.

Results. Under f.e. conditions the level of CP in blood serum of rats was statistically significantly different from intact animals (1st group) and amounted to 3.11 ± 0.02 μmol/L (2nd group). The biochemical study of the anti-inflammatory effect of celecoxib and caffeine on the content of CP inflammation marker showed that the study drugs (3rd and 4th groups) influenced CP content in blood serum of rats with varying efficacy and decreased it against f.e. (2nd group).

When celecoxib was administered alone (3rd group), only a tendency towards decrease in the level of CP in blood serum of rats was observed against f.e.

With solo-administration of caffeine (4th group), 1.6-fold decrease in the content of CP in blood serum of rats was observed against f.e., that did not differ statistically significantly from the reference drug. That means, caffeine effectively influenced decrease in the content of protein of the acute phase of CP inflammation in blood serum of rats under f.e. (2nd group).

Addition of caffeine to celecoxib (5th group) contributed to effective decrease in the content of CP in blood serum of rats, which is statistically significant against f.e. This composition acted more efficiently than the reference drug (6th group), the data obtained did not differ statistically significantly from the intact control (1st group), i.e., caffeine effectively potentiated the anti-inflammatory effect of celecoxib, and the pharmaceutical composition we created became the leader of our study.

Conclusions.

1. Results of biochemical studies on analyzing the anti-inflammatory effect of celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-pyrazol-1-yl]benzene sulfonamide)), caffeine (1,3,7-trimethylxanthine) and their pharmaceutical composition on the level of CP in blood serum of rats indicate that both pharmaceutical preparations affect the level of CP, but with different degrees of activity (caffeine > celecoxib).

2. Caffeine potentiates decrease in the level of CP with celecoxib in blood serum of rats under conditions of formalin edema, as a result of which the studied indicator normalizes, as evidenced by the absence of statistically significant differences between the 5th groups and the reference one (1st group).

3. The two-component pharmaceutical composition created by us, consisting of celecoxib and caffeine, is the leader in biochemical studies of the level of CP inflammation protein in blood serum of rats under formalin edema and acts more efficiently than the reference drug 2 (2 (2.6 dichlorophenylamino) phenyl) acetic acid.

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