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The effect of COX-2 inhibitor celecoxib and proton pump blocker lansoprazole on lipoperoxidation processes in heart tissue and gastric mucosa of streptozotocin-induced diabetic in rats

Wpływ inhibitora COX-2 celekoksybu i blokera pompy protonowej lansoprazolu na procesy lipoperoksydacji w sercu i śluzówce żołądka szczurów z cukrzycą indukowaną streptozotocyną

Diabetes mellitus is the most widespread metabolic disease nowadays. The factors making diabetes so extremely hazardous are the complications with which the disease is followed. The probability of complications increases with the poor glycemic control. A poor glycemic control is dangerous also because as shown by numerous data hyperglycemia it promotes the appearance of oxidative stress [7, 12]. Nitric oxide in diabetes posses a dual function – it generally has a positive effect on the vascular wall, but it also interacts with free radicals amplifying their effect. In diabetes, NO action and production is inhibited by several processes – by activation of protein kinase C, which produces its antagonist, by degradation of circulating NO, as well as by interfering with its interaction with receptors [11]. According to the fact that diabetes causes prolonged, topical inflammatory states, COX-2 activation takes place [1]. COX-2 produces prostaglandins, including thromboxane which has a well-known vasoconstrictive function and enhances platelets aggregation [2, 9]. The normally existing balance between thromboxane and prostacycline, which has opposite effects in diabetes is disturbed due to COX-2 overexpression. In diabetes, pH of gastric juice is always slightly higher than in the norm [3]. This provides additional information about the treatment with proton pump inhibitors (PPI). PPI (omeprazole, lansoprazole, rabeprazole) are the most effective drugs to treat peptic ulcer disease as well as gastro-oesophageal reflux disease.

The aim of the experiment was to to study changes in lipoperoxidation processes, the activity of the antioxidant protection system and NO content in heart and gastric mucosa of streptozotocin-induced diabetic rats, to study the action of selective inhibitor of COX-2 celecoxib and PPI – lansoprazole on oxidative processes during diabetes in rats.

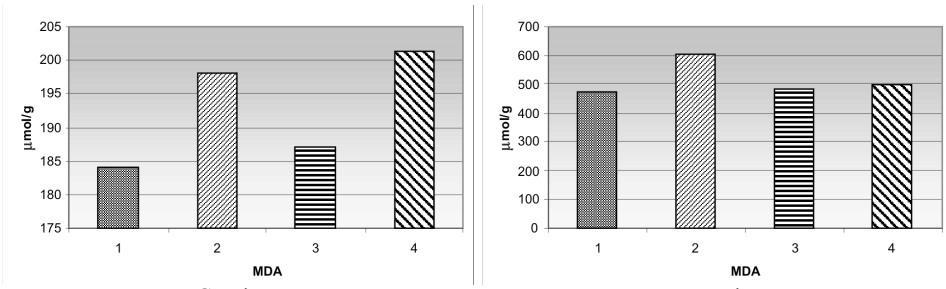
MATERIAL AND METHODS

The experiment was performed on 20 white rats during 28 days. They were divided into 4 groups. The animals of II, III and IV groups were provided with intraperitoneal injection of streptozocin in the dose of 60 mg per kg of body weight. After 14 days, diabetes mellitus developed (fasting blood glucose level rose to 15–16 mmole/l) and for the next 14 days the groups were growing in

similar conditions and treated as follows – the 1st group is healthy non-diabetic, the 2nd is non-treated diabetes, the 3rd is diabetes with celecoxib administration perorally in the dose of 10 mg/kg of body weight, provided daily. The 4th group is diabetic individuals with lansoprazole provided in a similar fashion to celecoxib, in the dose of 30 mg/kg of body weight. At the end of the experiment the rats were killed by decapitation and homogenates of their heart tissue and gastric mucosa were made. Lipoproxidation processes were evaluated by malonic dialdehyde (MDA) content [10], the activity of enzymes of the antioxidant protection system was evaluated on the basis of determination of SOD [8] and catalase [5]. Griess reagent was used to measure the content of NO [4]. In the processing of the obtained results, variation statistics method was employed and Student's criteria determined. All the experiments were performed in correspondence with the guidelines of the International Committee on Experimental Animals.

RESULTS AND DISCUSSION

MDA content in diabetic rats was considerably enhanced in both investigated tissues (gastric mucosa by 8% and heart tissue by 29%) (Fig. 1), indicating intensification of lipoperoxidation processes. These dates are such as stipulated in texts [1, 2].



Gastric mucosa Heart tissue

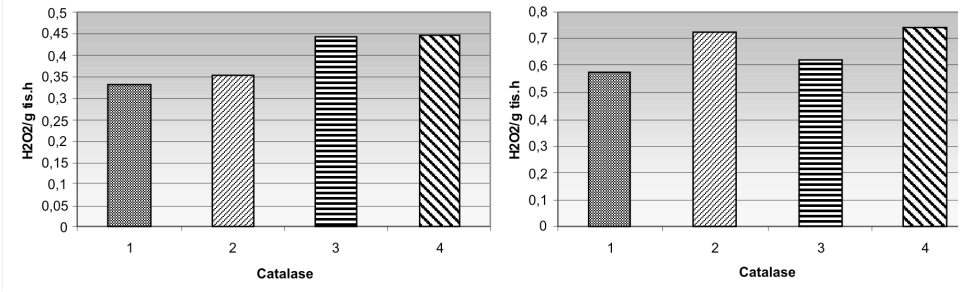
Fig 1. Content of MDA in gastric mucosa and heart tissue: 1 – control group, 2 – diabetes, 3 – diabetes+celecoxib, 4-diabetes+lansoprazole

Streptozotocin-induced diabetes caused an increase of catalase activity in heart by 26% ($p<0.05$) and the same tendency to the enlargement was observed in gastric mucosa (by 7%) (Fig. 2). The activity of SOD was also increased in heart tissue (by 39.5%) and gastric mucosa (by 33%) (Fig. 3).

Celecoxib administration caused a decrease of MDA production in comparison with diabetes in both tissues although it still remains higher than in control. NO concentration under COX-2 inhibition rose in gastric mucosa (by 75%, $p <0.01$) as well as in heart tissue (by 54%, $p <0.01$) and it was even higher than in the norm (Fig. 4). Catalase activity is increased in gastric mucosa (by 25%) and the same phenomenon took place in the tissue SOD activity (by 78%), while compared with diabetic state. On the other hand, in heart tissue the activity of both enzymes are lowered in comparison to diabetic state.

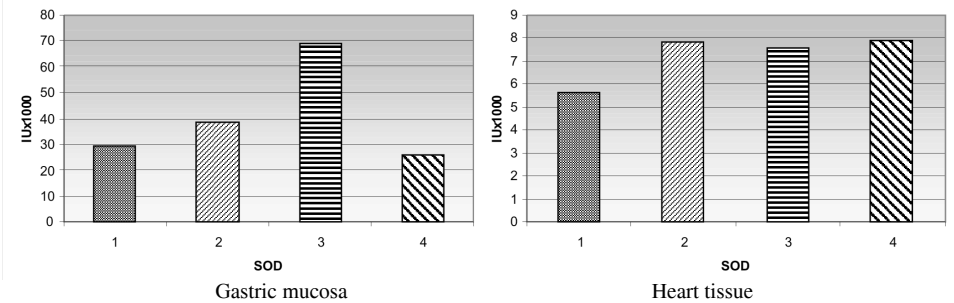
Lansoprazole application led to intensification of lipoperoxidation (Fig. 1), which can be caused by increase in pH unusual for stomach. In heart tissue, MDA concentration falls with a rate of 17%. NO level was doubled in heart tissue. Earlier, we observed this effect of PPI on NO content in heart tissue of intact animals [4]. The origin of this phenomenon is probably the fact that lansoprazole also inhibits other ATPases which belong to P-type, eg. Ca^{2+} and thus increases intracellular concentration of calcium, which in turn activates Ca^{2+}-dependent NOS. This increase of NO content may by harmful.

The activity of antioxidant protection system enzymes was always elevated under proton pump blockage; an exception is the decrease of SOD activity in gastric mucosa by 34% in comparison to diabetes.



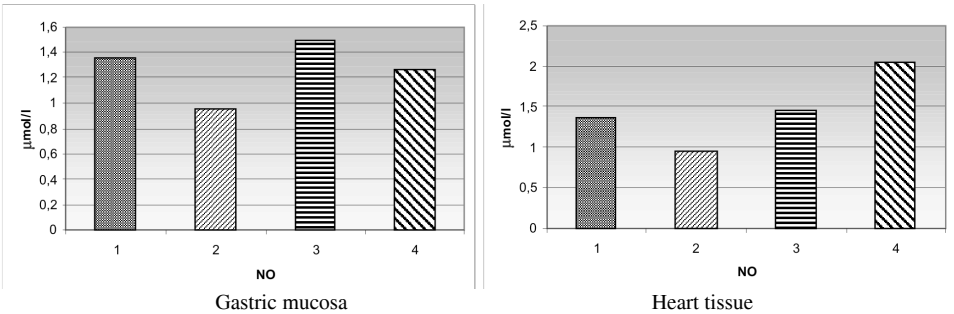
Gastric mucosa Heart tissue

Fig 2. Activity of catalase in gastric mucosa and heart tissue: 1 – control group, 2 – diabetes, 3 – diabetes+celecoxib, 4-diabetes+lansoprazole



Gastric mucosa Heart tissue

Fig 3. Activity of SOD in gastric mucosa and heart tissue: 1 – control group, 2 – diabetes, 3 –diabetes+celecoxib, 4 – diabetes+lansoprazole



Gastric mucosa Heart tissue

Fig 4. NO concentration in gastric mucosa and heart tissue: 1 – control group, 2 – diabetes, 3 –diabetes+celecoxib, 4-diabetes+lansoprazole

CONCLUSIONS

Experimental diabetes mellitus causes activation of oxidative stress in most tissues. Metabolic disorders, which occur under these conditions, are accompanied by intensification of lipoperoxidation as well as partial blockage of hydrochloric acid in stomach.

COX-2 inhibition had similar effects in both investigated tissues: it decreased lipoperoxidation as well as the formation of free radicals and increased the activity of the antioxidant protection system. Celecoxib administration caused an increase of NO content in heart tissue, which could be associated with the increase of NOS activity.

Proton pump inhibition led to a decrease of lipoperoxidation in gastric mucosa, caused by an abnormal decrease of acidity in stomach. Lansoprazole had diverse effects on NOS system in heart tissue and gastric mucosa. NO content was reduced in gastric mucosa, whereas in heart tissue it was increased almost 2 times.

Therapies of diabetes such as antioxidants that are targeted against oxidative stress remain our most promising approach in combating complications in diabetes.

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SUMMARY

The influence of COX-2 inhibitor celecoxib and proton pump blocker lansoprazole on lipoperoxidation, antioxidation defense and the content of nitrogen oxide in rats' gastric mucosa and heart tissue with streptosotocin diabetes was studied. The obtained results showed that lipoperoxidation processes were activated in diabetic animals and the activity of antioxidation protection enzymes increased. Inhibition of prostaglandins synthesis by COX-2 decreased oxidative stress in both investigated tissues. Proton pump blockage led to a sharp increase of NO content in heart tissue and a decrease of MDA content in gastric mucosa

STRESZCZENIE

Badano wpływ inhibitora COX-2 celekoksybu i blokera pompy protonowej lansoprazolu na lipoperoksydację, obronę antyoksydacyjną i zawartość tlenku azotu w śluzówce żołądka i sercu szczurów z cukrzycą streptozotocynową. Uzyskane wyniki wskazują na aktywację procesów lipoperoksydacji i wzrost aktywności enzymów ochrony antyoksydacyjnej. Hamowanie syntezy prostaglandyn przez COX-2 zmniejszało stres oksydacyjny w obydwu badanych tkankach. Blokada pompy protonowej prowadziła do znacznego wzrostu zawartości NO w sercu i spadku zawartości MDA w śluzówce żołądka.