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Mini Review

Biological Effects of N1-Methylnicotinamide

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Abstract

The search for new biologically active compounds is an urgent task of modern pharmacology and medicine. N_1-methylnicotinamide is a first metabolite of vitamin PP. Its biological properties were poorly understood last decades. Some studies have shown protective effect of N_1-methylnicotinamide on ischemia-reperfusion injury in the liver and skin pathology. The purpose of this work is to analyze literary and own data on the results of the use of N_1-methylnicotinamide for various pathologies.

Keywords: *N_1-Methylnicotinamide; Oxidative Stress; Liver; Ischemia-Reperfusion*

Introduction

The main requirement for newly developed substances is their effectiveness, safety and the breadth of biological effects, which is fully combined by the metabolites of nicotinamide (vitamin PP), and above all, N_1-methylnicotynamide (MNA). MNA is one of the main metabolites of nicotinamide, which is a substrate for the NAD+ biosynthesis, the regulator of enzymatic activity of redox processes, an inhibitor of cell proliferation and an expression modulator.

Nature and biology of N_1-methylnicotinamide

The MNA is synthesized mainly in the liver under the influence of the nicotinamide-N-methyltransferase enzyme (nicotinamide: S-adenosyl methionine methyltransferase; EC 2.1.1), which is then metabolized into N_1-methyl-2-piridon-5-carb cap and N_1-methyl-4-Piridon-3-carboxamide under the influence of cellular oxidase [1]. For a long time, the MNA was considered only a product of degrading nicotinamide, which is derived in urine and does not have biologically active properties. However, in 2003, the anti-inflammatory properties of the MNA were shown, which were confirmed in clinical studies in the treatment of dermatoses and skin burns, realized through its interactions with glycosaminoglycans on the surface of the blood vessel endothelium, which reduce the adhesion of pro-inflammatory cells and prevent their penetration into tissues with various dermatological diseases [2]. The modification of the molecule of the MNA by replacing one of the hydrogen atoms with a hydroxymethyl group leads to the formation of a compound, which also has antibacterial properties [3].

MNA is an analogue of the precursor of nucleotide cofactors of a series of oxidoreductase capable of replacing nicotinamide molecules in the reactions of the formation of NAD+ and NADH+ *in vivo*, which leads to selective suppression of oxidative phosphorylation in mitochondria [4]. *In vivo* and *in vitro* studies, it is shown that MNA in large doses (2 g/kg) reduces the content of NAD+ in muscle tissue and liver, reduces the ratio of NAD+/NADH in red blood cells, and can also increase the H_2O_2 level, and contribute to the potentiation of oxida-

tive stress during diabetes mellitus [5]. However, it is known that diabetes mellitus is accompanied by the activation of gluconeogenesis, glycolysis inhibition and tricarbonyl acid cycle, which creates a deficiency of oxidation substrates (substrate hypoxia). Under these conditions, the use of any metabolism activators in cells, in addition to glucose, will reduce the NAD+/NADH ratio and increase the likelihood of oxidative stress. The use of moderate doses of MNA (100 mg/kg) over 8 weeks contributed to a decrease in oxidative stress and prevented the deterioration of no-dependent vasodilation in diabetes in rats [6]. Despite some inconsistency of data on the effect of MNA in diabetes, the ability to modulate the redox potential of cells and the work of mitochondria is the fundamental property of any biologically active compound.

The role of N_1-methylnicotinamide pathological conditions

Disorders of the microcirculation and the functions of the endothelium are the component of the pathogenesis of many diseases and pathological conditions, including ischemic damage to the heart and brain, arterial hypertension, diabetes mellitus, endotoxemia, organs-reperfusion syndrome, etc. It has been established that the MNA causes a dose-dependent decrease in thrombosis in arterial vessels, inhibition of platelet aggregation and increased fibrinolysis simultaneously with an increase in plasma of the metabolite of prostacyclin - 6-keto-prostaglandin $F_{1\alpha}$ [7]. The influence of the MNA can be realized through endothelium-dependent mechanisms (cyclooxygenase-2 and prostacyclin) [8,9]. It is shown that the MNA has a powerful gastroprotective effect with stressful effects, reducing oxidative damage and improving tissue microcirculation [10]. MNA also shows a neuroprotective effect with ischemic and hypoxic damage to the brain [11]. It was revealed that as the endothelial function worsen the activity of Nicotinamide-N-methyltransferases and the endogenous concentration of the MNA increase, which is accompanied by a simultaneous increase in the activity of glutathione peroxidase [1], exerting a protective effect on the vessels and providing a regulatory role in reducing thrombosis and the inflammatory process in the cardiovascular system.

Endotoxemia and systemic inflammatory response can occur in severe bacterial infections, sepsis, burns, shock, extensive surgical interventions, severe injuries, etc. In experiments on rabbits, it has been established that the injection of lips leads to activation of free radical processes of lipid peroxidation (half), increasing the level of level homocysteine in the blood and a decrease in antioxidant protection parameters in the blood, aorta, heart, lungs, liver and kidneys, while the introduction of the way has significantly reduced the content of gum and homocysteine products while increasing the concentration of α-tocopherol and the activity of catalase in comparison with animals, which only introduced only LPS [12]. The relationship between the activity of nicotinamide-n-methyltransferase in adipose tissue and an increase in the level of homocysteine, which decreases after using the MNA [13], is shown. It has been established that the MNA reduces the level of transaminases in the blood, α-TNF and IL-4, which has a protective effect on the liver when modeling acute hepatitis using concavalin-A in mice [9]. In general, an experimental study of the anti-inflammatory effects of the MNA for endotoxemia and toxic hepatitis is consistent with the previously revealed properties of this compound confirmed in clinical studies in the treatment of dermatosis and skin burns [2].

Given the identified anti-inflammatory and antioxidant properties of the MNA, we studied the possibilities of using this compound to correct the syndrome of hepatic ischemia-reperfusion injury, which is usually accompanied by a violation of the prooxidant and antioxidant balance and the development of oxidative stress. It was established that the infusion of the MNA (100 mg/kg, i.p.) to the rats before start of hepatic ischemia leads to significant decrease in the activity of the lipid peroxidation processes (the content of the conjugated Dienes and the Schiff bases in the blood was lower by 59.9% ($p < 0.001$) and 72.1% ($p < 0.001$), respectively), Improving the antioxidant system indicators, as well as to reduce blood transaminase activity (ALT and AST by 49.6% ($p < 0.001$) and 45.1% ($p < 0.001$), respectively) at the end of the reperfusion period in relation to animals without this drug [14]. It is shown that the introduction of MNA improves the oxygen-binding properties of the blood in reperfusion period after hepatic ischemia, shifting the curve of dissociation of oxyhemoglobin to the left [15]. Studying the mechanism of the protective effect of MNA in hepatic ischemia-reperfusion, it was found that inhibiting both prostacyclin receptors and cystathionine-γ-lyase - enzyme responsible for endogenous production of hydrogen sulfide, is similar to the

protective effect of the drug [16]. Perhaps the protective effect of the many could be mediated by calcium-dependent activation of protein kinase B, the latter can directly induce cystathionine-γ-lyase and the formation of endogenous hydrogen sulfide [17,18]. In addition, the MNA is able to correct the impaired NO-synthetic function of the endothelium when it is damaged by pro-inflammatory cytokines [17].

Conclusion

Thus, analysis of literary and own research results revealed a wide range of biological effects of the MNA. The most important properties of the many can be considered anti-inflammatory, antithrombotic, vasoactive (vasodilator), redox-modulating, cytoprotective (antioxidant) compound effects. The ability to influence the processes of microcirculation and oxygen-binding properties of the blood, as well as the relative harmlessness of this compound makes it a promising tool for the correction of post-hypoxic conditions.

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