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PROSPECTS FOR THE JNK KINASE INHIBITORS USE IN THE TREATMENT OF DYSLIPIDEMIC CONDITIONS

Numerous works have been devoted to the JNK regulatory pathways studies since the disorders of JNK activity were observed during carcinogenesis, neurodegenerative processes, cardiovascular diseases, diabetes, etc. Accumulating evidence supports a potential role of the JNK kinases inhibitors in treatment of obesity, metabolic syndrome, diabetes, etc. This discussion devoted to the prospects for their use in treatment of dyslipidemia associated pathologies.

KEY WORDS: **JNK-kinase, JNK-kinase inhibitors, dyslipidemia.**

INTRODUCTION. c-Jun N-terminal kinases (JNK) are members of a large group of stress-activated serine/threonine mitogen-activated protein kinases (MAPK), which are involved in the regulation of important cellular processes such as proliferation, differentiation, apoptosis, inflammation, and more [6, 25, 28]. Numerous works have been devoted to the JNK regulatory pathways studies since the disorders of JNK activity were observed during carcinogenesis, neurodegenerative processes, cardiovascular diseases, diabetes, etc. This enzyme is considered as a potential therapeutic target for pharmacological approach to therapy of diseases associated with the JNK activation. Taking into account the fact that this issue has been widely discussed in different publications, we expect to clarify the JNK participation in the dyslipidemic states development, as well as to analyze the effectiveness of the most widely used inhibitors of JNK in experimental studies. This discussion can open the prospects for their use in treatment of dyslipidemia associated pathologies.

DISCUSSION. **Jun amino-terminal kinases.** In mammals, JNKs are encoded by three different genes (JNK1, JNK2 and JNK3). Multiple molecular forms result from alternative splicing, thereby increasing the amount of 10 different protein products from 46 kDa to 55 kDa [26]. JNK1 and JNK2 are found in various tissues, the expression of JNK3 is restricted mainly in the brain, heart and testicle.

Structure of the JNK kinases is well studied. They have a typical structure characteristic of eukaryotic protein kinases: consist of two domains. N-terminal domain is rich of β-structures and C-terminal domain rich of α-helices. These two fragments were joined together site, which interacts with the JNK substrate. ATP molecules also bind near the domain surface [6]. All these structures have been identified for the inactive forms of JNK. Important changes in the structure were observed after activated by phosphorylation of the enzyme.

Inflammatory signals, reactive oxygen species, ultraviolet radiation, protein synthesis inhibitors and a variety of stress stimuli activate JNK. Activation may occur through disruption of the conformation of sensitive protein phosphatase enzymes since specific phosphatases inhibit the activity of JNK.

JNK signaling pathway. JNKs are activated by MAPK kinases, such as MKK-4, MKK-6 and MKK-7 [23]. These kinases in turn are activated by MAPK3 and, such as ASK1 – the adjustable kinase 1 – which is also known as a MAP3 kinases 5, the mixed lines of kinases (MLKs): MLK1, MLK2 and MLK3, MAP/ERK (the kinase regulated by extracellular signals) a kinase a kinase 1 – MEKK1, MEKK4 and transforming factor of growth (TGF)-β-activated kinase 1 – TAK1. JNK/MAP3 alarm ways are activated by MAP4 kinases which are connected with various cellular receptors sensitive to stress and inflammation, including death-receptors (Fas), receptors to inflammatory cytokines, tumor necrosis factor receptors - TNF-α and TGF-β, the receptors connected with G-protein (GPCRs) and receptors of anti-genes [25]. Signals are transmitted to JNK/MAP4 kinase through effector molecules and tyrosine kinases receptors and/or G-protein-coupled signal ways.

ASK1 is connected with stress receptors, such as TNF-α receptors and Fas, and in turn are activated by thioredoxin binding to TNF receptor-associated factor 2 or proteins associated with death-domains [3].

At least 50 proteins have been identified as JNK substrates. These proteins control multiple cellular processes, acting either as transcription factors or by controlling protein degradation, localization, and signaling. JNK substrates include c-Jun, JunB, JunD, activating transcription factor 2, p53, c-Myc, serum response factor, insulin receptor substrate-1, JNK interacting protein 1 JIP1, 14-3-3, Sab SH3BP5, Bcl-2, Bcl-xL, Bid, Bim, Bad, Bax, and Mcl-1 [6, 25]. Among these substrates, c-Jun is a representative target of JNKs. c-Jun forms dimeric complexes with JunB, JunD, or Fos to form the transcription factor activator protein (AP)-1, whereas SRF controls expression of the Fos proteins [20].

JNK1 is involved in apoptosis, neurodegeneration, cell differentiation and proliferation, inflammation and cytokine production mediated by AP-1 (activation protein 1) such as RANTES, IL-8 and GM-CSF [6, 25, 26, 28].

JNK mediates the dyslipidemia states development. JNK activity, which is mainly related to the JNK1 isoform, is increased in obese mice. In response to a high fat diet or in the context of genetically obese rodents, JNK1-null animals gain less body weight and are less prone to altered insulin sensitivity [1]. Liver-specific down-regulation of JNK signaling improves insulin responsiveness in animal models of type 2 diabetes.

A functional role for JNK1 in obesity was shown by the finding that standard or high fat diet-fed jnk1–/– but not jnk2–/– mice had decreased weight gain attributed to a reduction in adipose tissue mass. JNK1 null mice also had decreased serum glucose and insulin levels and increased hepatic insulin signaling, indicating improved insulin sensitivity [15]. Effects on hepatic lipid accumulation were not examined. Although these studies suggested no JNK2 involvement in obesity and insulin resistance, the ability of JNK2 to oppose JNK1 phosphorylation of c-Jun suggested that the effect of a loss of JNK2 may be compensated for by increased JNK1 function. To address whether JNK2 contributed to this metabolic phenotype, jnk2 null mice lacking one jnk1 allele were examined. Mice lacking one jnk1 and both jnk2 alleles were protected from HFD-induced obesity but jnk1+/– mice were not, indicating that JNK2 contributed to obesity.

Palmitic acid but not oleic acid induced insulin resistance in L6 myotubes through JNK and insulin receptor substrate 1 Ser307 phosphorylation. Inhibitors of ceramide synthesis did not block insulin resistance by palmitic acid [19].

Obesity is associated with an increased risk of nonalcoholic fatty liver disease (NAFLD). Steatosis, the hallmark feature of NAFLD, occurs when the rate of hepatic fatty acid uptake from plasma and de novo fatty acid synthesis is greater than the rate of fatty acid oxidation and export. Although the mechanisms for development of steatosis and chronic liver injury in NAFLD remain unclear, recent investigations have indicated that overactivation of JNK is critical to this process [28].

Investigations in methionine- and choline-deficient (MCD) diet-induced murine steatohepatitis demonstrated that increased hepatic JNK, c-Jun and AP-1 signaling occurred in parallel with the development of lipid overaccumulation and hepatitis [21]. The MCD diet model of NASH is limited by the lack of the extrahepatic manifestations of the metabolic syndrome including obesity, dyslipidemia and peripheral insulin resistance [19].

Cytokines and ROS activate JNK, IKK-β, PKC and perhaps other stress- and inflammation-activated kinases in the pathogenesis of ROS-induced insulin resistance [13]. As JNK-1 deficiency results in reduced adiposity and improved insulin sensitivity, this also may be a key regulator of the OIC. Thus, all these kinases might be attractive pharmacological targets for increasing insulin sensitivity.

Initial data suggesting a role for JNK in atherosclerosis were based on observations that the macrophages and smooth muscle cells of human and animal model atheromatous plaques had prominently activated JNK signaling [16]. Further evidence was provided by Ricci et al. [24] by creating mice with macrophage-specific ablation of two of the JNK family members, JNK1 and JNK2, in an ApoE-null background.

Since JNKs comprise a central node in the inflammatory signaling network, it is not surprising that hyperactivation of JNK signaling is a very common finding in a number of disease states including cancer, inflammatory and neurodegenerative diseases. A significant body of genetic and pharmacological evidence suggests that inhibitors of JNK signaling may provide a promising therapeutic strategy: JNK3 knockout mice exhibit amelioration of neurodegeneration in animal models of Parkinson's and Alzheimer's disease [33]. JNK1 phosphorylates IRS-1, a key molecule in the insulin-sensing pathway which down-regulates insulin signaling and JNK1 knockout mice are resistant to diet-induced obesity. JNK2, often in concert with JNK1, has been implicated in the

pathology of autoimmune disorders such as rheumatoid arthritis and asthma [30]. A recent study suggests that JNK2 may also play a role in vascular disease and atherosclerosis [9]. However, to date, no inhibitors of JNK have been approved for use in humans.

JNK inhibitors and their application. Numerous small molecules from a variety of scaffolds such as indazoles, aminopyrazoles, aminopyridines, pyridine carboxamides, benzothien-2-ylamides and benzothiazol-2-yl acetonitriles, quinoline derivatives, and aminopyrimidines have been reported to act as selective ATP-competitive JNK inhibitors [22]. Despite this plethora of compounds, many exhibit poor kinase selectivity and/or do not inhibit the phosphorylation of well-characterized substrates of JNK in cells. For example, one of the earliest and still most widely used inhibitors is the anthrapyrazolone, SP600125 which exhibits exceptionally low specificity for JNK and should only be used in combination with other tools to rule-out a potential role for JNK in a particular process [11]. Other reported JNK inhibitors such as AS601245 only inhibit c-Jun phosphorylation at high concentrations which is likely due to a combination of limited cell penetration, ATP concentration and differences between biochemical and cellular sensitivities to JNK inhibitors.

There are mainly 3 types of inhibitors thoroughly studied up to now. The first is the ATP-competitive inhibitor of the JNK pathway such as CEP-1347 and SP600125. They occupy the ATP-binding site of the protein kinase, which is structurally similar in all kinases, so the phosphorylation of substrates is blocked.

In addition to the ATP-binding site, other sites on the kinase can also provide the target for inhibition, so the second kind of inhibitor targets the substrate-binding site. Based on this mechanism, many peptide inhibitors and dominant-negative mutants against kinases have been designed.

The third kind of inhibitor targets the allosteric regulatory sites. Either peptides or chemical non-peptides can be used if they can bind to the regulatory sites and block the phosphorylation.

SP600125 (Anthra(1,9-cd)pyrazol-6(2H)-one) is a reversible ATP-competitive inhibitor with >20-fold selectivity vs. a range of kinases and enzymes tested. In cells, SP600125 dose dependently inhibited the phosphorylation of c-Jun, the expression of inflammatory genes COX-2, IL-2, IFN-gamma, TNF-alpha, and prevented the activation and differentiation of primary human CD4 cell cultures [27].

SP 600125 suppressed Cd-induced pancreatic в-cell apoptosis, but not ERK1/2 and p38-MAPK inhibitors [7]. Cd induces pancreatic β-cell injury via an oxidative stress downstream-mediated JNK activation-triggered mitochondria-regulated apoptotic pathway. However, this JNK inhibitor did not suppress ROS generation in Cd-treated cells.

Hyperglycemia increased iNOS mRNA in cultured C57BL/6J, and SP600125 abolished this effect. Hyperglycemia increased iNOS-luciferase activities, and SP600125 also blocked this effect [32].

Lipotoxicity plays an important role in underlying mechanism of type 2 diabetes. Prolonged exposure of pancreatic beta-cells to elevated levels of fatty acid is associated with beta-cell apoptosis. Exposure of pancreatic β-cells to ghrelin caused a rapid activation of protein kinase B (PKB) and inhibition of JNK under lipotoxic state. SP600125 enhanced protective effect of ghrelin [14] and blocked palmitate induces autophagy in pancreatic в-cells.

The endemic occurrence of obesity and the associated risk factors that constitute the metabolic syndrome have been predicted to lead to a dramatic increase in chronic liver disease. Non-alcoholic steatohepatitis (NASH) has become the most frequent liver disease in countries with a high prevalence of obesity. Inhibition of JNK by SP600125 significantly reduced palmitate-induced steatosis, ROS accumulation, and apoptosis, indicating that the protective effect against palmitate-induced cellular damage result from blocking ROS-activated JNK signaling [2]. At the same time there are a number of problems in application of inhibitors of this type. Effects obtained on the isolated cells are not always reproduced in conditions in vivo.

MCD and control diet fed C57BLKS/J mice were treated with SP 600125 for 2 weeks. SP600125 decreased both JNK2/3 and JNK1 protein levels. As expected, mice fed the MCD diet developed steatohepatitis; however, the severity was not affected by SP600125. Serum ALT, hepatic triglycerides and the degree of steatohepatitis on histology remained unchanged in MCD fed mice treated with SP 600125 [10].

AS601245 (1,3-benzothiazol-2-yl (2-{[2-(3-pyridinyl) ethyl] amino}-4 pyrimidinyl) acetonitrile), also inhibits the JNK, has neuroprotective properties in animal models of stroke. Some studies show that AS601245, in addition to its ability to protect neuronal cell bodies, also prevents loss of neuritis, decreases astrogliosis and improves long-term memory deficits induced by cerebral ischemia [3].

In vivo experiments showed that AS601245 administration provided significant protection against the delayed loss of hippocampal CA1

neurons in a gerbil model of transient global ischemia [4]. Results obtained demonstrated that the combined treatment with rosiglitazone and AS601245 increases the anticancer effects of the two substances in colon cancer cells.

AS601245 didn't affect under dyslipidemic states conditions in experimental animals. However, this inhibitor showed positive results in conditions in vitro and it reveals anti-inflammatory action that makes it perspective agent for dyslipidemia disease therapy.

CC-930 also known as Tanzisertib, is described as a potent, selective, and orally active JNK inhibitor with potential antifibrotic activity and also was used in intervention treatment for type 1 diabetic nephropathy in hypertensive rats [12]. At week 16 of diabetes in rats CC-930 in dose 60 mg/kg reduced macrophages and ccl2 mRNA levels in diabetic kidneys.

Curcumin is a compound isolated from the turmeric plant and primarily used as a natural yellow pigment. It has a variety of biological activities and pharmacological actions, such as anti-inflammatory, anti-carcinogenic, and antivirus properties, as well as promising clinical applications due to its low toxicity. Most inflammatory stimuli are known to activate three independent MAPK pathways, leading to activation of p44/42 MAPK (also called ERK1/ERK2), JNK, and p38 MAPK pathway. Chen et al. [8] found that curcumin inhibits JNK activation induced by various agonists including PMA plus ionomycin, anisomycin, UV-C, gamma radiation, TNF, and sodium orthovanadate.

Although curcumin does not directly interact with NK kinase its synthetic analogs are specific inhibitors of this enzyme.

It was shown that a curcumin analogue *C66* (2E,6E)-2,6-bis(2-(trifluoromethyl)benzylidene)cyclohexanone) exhibited strong inhibitory effect on LPS-induced inflammatory cytokine expression in mouse macrophages [18]. It also exhibited anti-inflammatory actions in HG-stimulated macrophages and renoprotective effects in diabetic rats [17].

C66 was buried inside JNK active site and achieved two hydrogen bonds with Arg72. C66 also interacted with the hydrophobic residues in this site in the most energetically favorable simulation.

Another curcumin analogue *B06* exhibited an anti-inflammatory activity compared to curcumin. In vitro, pretreatment with B06 at a concentration of 5 мМ significantly reduced the high-glucose-induced overexpression of inflammatory cytokines in macrophages. This effect of B06 is associated with its inhibition of JNK/nuclear factor κB activation. In vivo, despite that B06 administration at 0.2 $mg \cdot kg^{-1} \cdot d^{-1}$ for 6 weeks did not affect the blood glucose profile of diabetic rats [5], the B06-treated animals displayed significant decreases in inflammatory mediators in the serum, kidney, and heart and renal macrophage infiltration. This was accompanied by attenuation of diabetes-induced structural and functional abnormalities in the kidney and heart. Taken together, these data suggest that B06 might be a potential therapeutic agent for diabetic complications via an anti-inflammatory mechanism.

Inhibition of JNK kinases: potential benefit versus risks. JNK inhibitors gives good results in model experiments, allowing the neck to discuss further enhance the prospects of their use of human clinical trials. At the same time there are still some obstacles. Possible problems with inhibiting JNK may be due to the important role it plays in other cellular functions such as cell proliferation, cell differentiation, the inflammatory response, and apoptosis.

Enthusiasm for the use of JNK inhibitors has been dampened by concerns about toxicity. SP600125 caused developmental abnormalities during zebrafish organogenesis starting at 1.25 μm and the defects were exacerbated with increasing concentrations [29].

Another important aspect of the use of inhibitors is their specificity, because with a few exceptions, for example, SP600125, the majority of newly synthesized or isolated inhibitors are active against other kinases. Based on the in vitro C66 directly targets JNK with a high selectivity on ERK. Using inhibitors that are active against various kinases and many signaling pathways require additional modeling experiments, as well as compliance with greater caution when moving to clinical trials.

CONCLUSION. Accumulating evidence supports a potential role of the JNK kinases inhibitors in treatment of obesity, metabolic syndrome, diabetes, etc. However, taking into account their possible toxicity, affinity for the whole group of signaling kinases, as well as the involvement of a wide variety of data kinases in signaling pathways in the cell, risk-benefit considerations have precluded their use in clinical trials in humans. At the same time, search and study of new selective inhibitors of kinases can be extremely promising in the treatment of dyslipidemic conditions and diseases mediated by JNK kinase participation.

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ПЕРСПЕКТИВИ ЗАСТОСУВАННЯ ІНГІБІТОРІВ JNK-КІНАЗ ПРИ ЛІКУВАННІ ДИСЛІПІДЕМІЙ

Резюме

Велику кількість публікацій присвячено вивченню регуляторних метаболічних шляхів JNK-кіназ. Підвищену активність JNK-кіназ спостерігають при канцерогенезі, нейродегенеративних процесах, захворюваннях серцево-судинної системи, діабеті тощо. Численні експериментальні дані підтверджують потенційну роль інгібіторів JNK-кіназ у корекції ожиріння, метаболічного синдрому, діабету та інших захворювань. Даний огляд висвітлює перспективи їх застосування при лікуванні патологій, які супроводжуються дисліпідеміями.

КЛЮЧОВІ СЛОВА: **JNK-кінази, інгібітори JNK-кіназ, дисліпідемії.**

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ПЕРСПЕКТИВЫ ПРИМЕНЕНИЯ ИНГИБИТОРОВ JNK-КИНАЗ ПРИ ЛЕЧЕНИИ ДИСЛИПИДЕМИЙ

Резюме

Большое количество публикаций посвящено изучению регуляторных метаболических путей JNK-киназ. Повышенную активность JNK-киназ наблюдают при канцерогенезе, нейродегенеративных процессах, заболеваниях сердечно-сосудистой системы, диабете и др. Многочисленные эксперименты подтверждают потенциальную роль ингибиторов JNK-киназ в коррекции ожирения, метаболического синдрома, диабета и других заболеваний. Данный обзор освещает перспективы их применения в лечении патологий, которые вызваны дислипидемиями.

КЛЮЧЕВЫЕ СЛОВА: **JNK-киназы, ингибиторы JNK-киназ, дислипидемии.**

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