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Multiple role of histamine H_1-receptor–PKC–MAPK signalling pathway in histamine-stimulated nerve growth factor synthesis and secretion

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Abbreviations:
AP-1, activator protein-1
CNS, central nerve system
ERK, extra-cellular signal-regulated kinase
IL, interleukin
JAK, Janus kinases
JNK, JUN-N-terminal kinase
MAPK, mitogen-activated protein kinase
MEK1, MAPK kinase 1
NGF, nerve growth factor
PI3, -3 kinase
PKC, protein kinase C
TPA, 12-O-tetradecanoylphorbol-13-acetate
TRE, TPA-response element

ABSTRACT

Histamine is a potent stimulator of nerve growth factor (NGF) production in the central nerve system and in the periphery as well. In this review, the biochemical mechanisms of histamine-stimulated NGF synthesis and secretion, and interactions between histamine, interleukin-1beta, and interleukin-6 are discussed. The main signalling pathway, involved in the stimulation of NGF production by histamine, includes activation of histamine H_1-receptor, stimulation of Ca^{2+}-dependent protein kinase C and mitogen-activated protein kinase. The same signalling pathway is involved in the interactions between histamine, interleukin-1beta, and interleukin-6, where NGF secretion is amplified. Whereas histamine and interleukin-1beta cause additive stimulatory effect on NGF secretion, interaction between histamine and interleukin-6 causes a long-term synergism.

Thus, activation of histamine H_1-receptor–protein kinase C–mitogen-activated protein kinase signalling pathway plays a crucial role not only in the direct stimulation of NGF secretion by histamine, but also in the indirect stimulation via different types of interactions between histamine, interleukin-1beta, and interleukin-6, which may have important therapeutic implications in modulation of NGF production.

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TrkA, tropomyosin-receptor kinase A
STAT, signal transducers and activators of transcription

1. Introduction

Nerve growth factor (NGF) is essential to organise and maintain neurons functionally. It plays a key role in the induction of neuronal differentiation, promotion of neuronal survival and the prevention of apoptosis in neurons of both central and peripheral origin [1,2]. In addition to its neurotrophic activity, NGF stimulates a wide variety of inflammatory cells and importantly contributes to the creation of immune response and inflammation [2,3]. NGF is involved in certain neurodegenerative disorders in the central nerve system (CNS), like Alzheimer's disease and Down syndrome, and different inflammatory diseases at the periphery as well [3,4]. Among them, asthma [5], psoriasis [6], allergic contact dermatitis [7], and atopic dermatitis [8] have been reported.

The NGF production is widespread throughout the body. The major sources of NGF in the CNS are neurons and astroglial cells [2], whereas the NGF production in the periphery occurs in different types of cells. They involve inflammatory cells as T and B lymphocytes, mast cells, eosinophils, monocytes, and structural cells like cutaneous, bronchial, and intestinal epithelial cells, cutaneous and pulmonary fibroblast cells, and bronchial, vascular, and vesical smooth muscle cells (for review see [9]). When synthesized, NGF can be stored and secreted by a regulated pathway, i.e. consecutive secretion from neurons, or it is secreted constitutively without storage [10]. The synthesis and secretion of NGF is regulated via various receptors and molecular mechanisms which involve four main signalling pathways: activation of adenylate cyclase, phospholipase C beta, phospolipase A_2, and mobilisation of Ca^{2+} ions [4,11]. Several substances, such as neurotransmitters, growth factors, cytokines, and steroids participate in this process. In this sense, the NGF production can be amplified following treatment of the cells with dopamine, adrenaline, isoproterenol [12,13], derivates of 1,4-benzoquinone [14], 12-O-tetradecanoylphorbol-13-acetate (TPA) [15], interleukin (IL)-4 and IL-5 [16], serotonin [17], and some growth factors [18]. Furthermore, histamine, IL-1beta, and IL-6 have also been recognized as potent stimulators of NGF synthesis and secretion in the CNS and periphery as well [19–22].

NGF forms covalent homodimers that activate two types of receptors: the tropomyosin-receptor kinase A (TrkA) which has intrinsic tyrosin-kinase activity and binds NGF selectively [23], and the $p75^{NTR}$ receptor for neurotrophins, which binds all neurotrophins and pro-neurotrophins, in particular pro-NGF ([24,25], for review see [9]). In humans, the TrkA receptor is expressed on cells throughout the nervous system as well as on structural cells and other non-neuronal cells in the immune and neuroendocrine systems [1,2,26]. When binds to the TrkA receptor, NGF induces receptor homodimerisation, which initiates kinase activation and transphosphorylation [27]. This kinase activation involves the small G proteins: G Ras, Rac, Rap-1, vav, the phospholipase C, protein kinases C (PKC), and phosphatidyl-inositol-3 kinase (PI3 kinase). Then the mitogen-activated protein kinase (MAPK) pathways are activated: extra-cellular signal-regulated kinase (ERK) by the small G proteins; ERK, p38, and JUN-N-terminal kinase (JNK) MAPK by PKC; and p38 and JNK by PI3 kinase. PI3 kinase in turn induces activation of protein kinase B and PKC. NGF activation of the TrkA receptor induces cell proliferation, differentiation, and survival; it inhibits apoptosis, increases neuronal excitability and induces mediator release from cells expressing TrkA (for review see [9]).

The $p75^{NTR}$ receptor belongs to the family of death receptors and shows strong homology with the tumor necrosis factor-alpha p75 receptor [28]. Stimulation of the $p75^{NTR}$ by NGF first induces homodimerisation of the receptors, thereby initiating activation of the adaptive proteins that bind to the extracellular domain, activation of an atypical PKC iota, involvement of the transcription factor NF-kappaB, or synthesis of ceramides, and then activation of the JNK MAPK. Signalling pathways activated by the $p75^{NTR}$ receptors appear to promote cell survival as well as apoptosis in the presence or absence of TrkA receptor expression at the cell membrane (for review see [9]).

Most inflammatory and structural cells in humans express both, Trk A and $p75^{NTR}$ NGF receptors. Recent observation of TrkA and $p75^{NTR}$ NGF receptor expression at the cell membrane of structural cells suggests NGF autocrine regulation in these cells [9]. Furthermore, the expression of TrkA and $p75^{NTR}$ receptors is increased in certain inflammatory diseases like atopic dermatitis [29] and myasthenia gravis [30], where the role of NGF is important.

Several immunomodulators are involved in the creation of immune response. Among them, histamine, IL-1beta and IL-6 play an important role. Besides their stimulating effect on NGF production, histamine, IL-1beta and IL-6 have common interactions in different immunological responses [31]. This review is focuses on the biochemical mechanisms of histamine-stimulated NGF synthesis and secretion, and interactions between histamine, IL-1beta, and IL-6 in this process. The role of histamine receptors, PKC and MAPK in the stimulation of NGF production is highlighted.

2. The role of histamine H_1-receptor–PKC–MAPK signalling pathway in histamine-stimulated NGF synthesis and secretion

Histamine is biogenic amine, widespread throughout the body. The major sources of histamine in the CNS are histaminergic neurons and mast cells, whereas inflammatory cells (mast cells, basophils, and monocytes) in the periphery synthesize and store the majority of histamine. Histamine exerts its actions via four receptor types: histamine H_1-, H_2-,

H_3-, and H_4-receptor. They all belong to the group of receptors with seven trans-membrane domains coupled to G-protein-mediated signal-transduction pathways, and are expressed widely in different tissues through the body (for review see [32]).

We showed in the past that histamine is a potent stimulator of NGF production from astroglial cells in primary culture [33]. This finding firstly indicated the involvement of histamine in the regulation of NGF production. Recently, the stimulatory effect of histamine on NGF synthesis and secretion from human keratinocytes has been found [3], which indicates the involvement of histamine in diseases, where the production of NGF is important, not only in the CNS but also at the periphery.

In the receptor studies on cultured astrogial cells we revealed the expression of both, histamine H_1- and H_2-receptors [35]. Both types of receptors were found also in human keratinocytes [3]. However, the stimulatory effect of histamine on NGF production is effectively blocked only by histamine H_1-receptor antagonists/inverse agonists in cultured astroglial cells [19,34] and human keratinocytes as well [3], whereas histamine H_2-receptor antagonists do not influence the histamine-stimulated NGF production in any type of these cells. Similarly, H_3- and H_4-antagonists do not show any effect on histamine-induced NGF production in cultured astrocytes and/or human keratinocytes as well [3,34], however there is also no data about the expression of H_3- and H_4-receptors in any type of these cells, so far. These results show that histamine H_1-receptor plays a crucial role in the signal-transduction pathway, responsible for histamine-stimulated NGF synthesis and secretion from cultured astrocytes and human keratinocytes, although the role of other histamine receptor subtypes is not excluded in the regulation of NGF production in other cells.

It is known that stimulation of histamine H_1-receptor activates phospholipase C beta which catalyses the hydrolysis of phosphatidylinositol 4,5-biphosphate to form inositol-1,4,5-trisphosphate and diacylglycerol. Inositol-1,4,5-trisphosphate released into cytoplasm causes the mobilization of Ca^{2+} ions from intracellular stores, whereas diacylglycerol activates PKC [36]. In the regulation of NGF synthesis and secretion, different PKC isoforms can participate in the transmission of the signal [37]. For the NGF production, evoked by histamine, PKC alpha isoform is crucial [38]. It belongs to the conventional PKC group which depends on both, diacylglycerol and Ca^{2+} ions. The same group of PKC was also shown to be sensitive to phorbol esters, which are potent stimulators of NGF mRNA expression and synthesis in astroglial cells [4,11]. PKC alpha plays an important role in the ability of histamine to transduce the signal to the nucleus [36]. We found that the stimulation of PKC alpha, through histamine H_1-receptor, in the further step activates the MAPK pathway [38], which is consistent with the previous findings, where diacylglycerol-dependent PKC isoform can stimulate the MAPK activation [36]. The signal is transduced via activation of mitogen-activated protein kinase kinase 1 (MEK1) [38] which is able to activate several downstream MAPK pathways [39].

Furthermore, it has been found that histamine enhances NGF secretion, mRNA expression, and promoter activity in human keratinocytes. Histamine enhances transcriptional activity and DNA binding of activator protein-1 (AP-1) at the two TPA-response elements (TRE) which may act as enhancer elements for NGF transcription [3,40]. It shifted the TRE-AP-1 composition from c-Jun homodimers to c-Fos/c-Jun heterodimers. Histamine transiently induces c-Fos mRNA expression via ERK activation [3], which is known to be associated with the regulation of proliferation, anti-apoptosis, differentiation, and gene expression (i.e. cytokine gene expression) [41,42]. On the contrary, c-Jun mRNA expression in keratinocytes is constitutive, and is not altered by histamine [3].

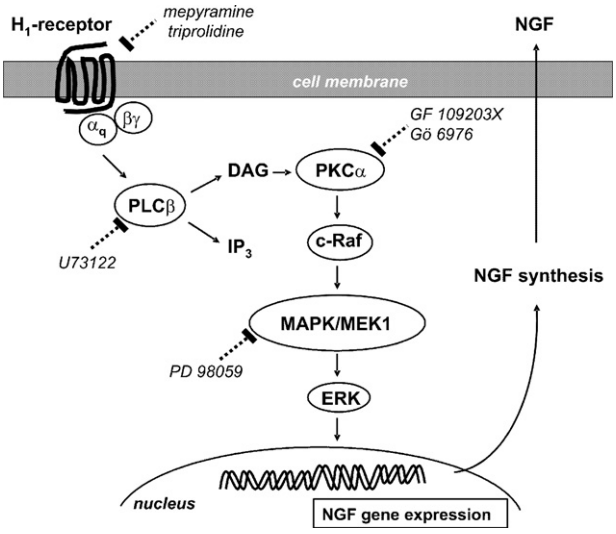

Fig. 1 – Proposed model of the signalling pathway in histamine-stimulated NGF production. Histamine induced NGF synthesis and secretion is triggered through the stimulation of histamine H_1-receptor which in further steps leads to the activation of phospholipase C beta, PKC alpha, and MEK1 which finally activates ERK cascade to the nucleus. The signal transmittion can be blocked by histamine H_1-receptor antagonists/inverse agonists (mepyramine, triprolidine), or PLC inhibitor U73122, or PKC inhibitors (GF 109203X, Go 6976), or MEK1 inhibitor (PD 98059).

PKC is also known to phosphorilate and activate c-Raf, and the activated c-Raf may further phosphorilate and activate MEK1 catalyzing ERK phosphorylation [3,43]. Thus, the activation of histamine H_1-receptor may trigger the signalling cascade of PLC–PKC–c-Raf–MEK1–ERK, and resultantly induce c-fos transcription and NGF gene expression (Fig. 1).

3. Histamine–cytokines interactions in the NGF synthesis and secretion: the role of histamine H_1-receptor–PKC–MAPK signalling pathway

Histamine plays a crucial role in the modulation of inflammatory and immune reactions. Besides, it also modifies cytokine actions. Both, the expression and effects of certain cytokines, can be influenced by histamine. Not only are cytokines influenced by histamine, but the release of histamine is also modulated by cytokines. Therefore, bidirectional links may be envisaged between cytokines and

histamine, modulating the actions of each other (for review see [32]). Although interactions between histamine, IL-1beta and IL-6 are well described in several physiological and pathological responses, they remained unclear in the regulation of NGF production, so far.

3.1. *Histamine–IL-1beta interaction*

IL-1beta possesses a strong stimulatory effect on NGF production. The NGF synthesis, evoked by IL-1beta, is mediated via activation of IL-1 receptors. In the signal transmission, distinct protein kinases and phosphoprotein-phosphatases are involved [44]. Stimulation of IL-1 receptor leads to signalling cascade that activate transcription factor NF-kappa B and three different groups of MAP kinases: JNK, p38, and ERK, and their downstream signal transducers and activators of transcription proteins c-Jun and c-Fos [45]. IL-1beta can also generate PKC cascade in certain transcription processes and acts synergistically with PKC-activators phorbol-esters in the stimulation of NGF synthesis and secretion [4,46].

We found that simultaneous treatment of the astroglial cells in primary culture with histamine and IL-1beta significantly increases NGF secretion from cultured astrocytes after 24 h of incubation, in comparison to the secretion, reached by either histamine or IL-1beta alone. The effect of histamine and IL-1beta is dose-dependent and additive [47]. It closely correlates with findings, where TPA, which is also potent stimulator of PKC, and IL-1beta, gave an additive increase in NGF mRNA content and NGF secretion from cultured astrocytes [4,46]. TPA enhances the NGF synthesis through the PKC-stimulated activation of AP-1 which is also involved in the NGF synthesis, evoked by histamine [3,4].

Histamine H_1-receptor antagonists/inverse agonists mepyramine and triprolidine both effectively block the additive effect of histamine and IL-1beta to the level of the stimulation of NGF secretion by IL-1beta alone, but they have no effect on NGF secretion, stimulated by IL-1beta alone. Similarly, PKC inhibitors (GF 109203X, which is selective for the conventional PKC isoform group and Go 6976 which is Ca^{2+}-dependent, PKC alpha isoform selective inhibitor), and MEK1 inhibitor (PD 98059), suppress the additive effect of histamine and IL-1beta, but fail to inhibit the stimulatory effect of IL-1beta [47]. According to these findings, down-regulation of PKC-activity also diminishes the additive effect of PKC-stimulator TPA and IL-1beta, but does not influence the stimulatory effect of IL-1beta [46]. In fact, IL-1beta is able to activate NGF gene expression and secretion by a distinct signalling pathway, where stimulation of PKC is not important [46].

These findings indicate that histamine and IL-1beta stimulate NGF synthesis and secretion via different signalling pathways, however, stimulation of histamine H_1-receptor and activation of PKC-MAPK/MEK1 signalling pathway is crucial in the interaction between histamine and IL-1beta, where additive effect occurs.

3.2. *Histamine–IL-6 interaction*

Among cytokines, IL-6 also contributes in the regulation of NGF production. The stimulation of NGF synthesis is mediated by a specific receptor system, composed of a binding site (IL-6 receptor) and a signal-transducing component, gp/30. Activation of the receptor system leads to cytoplasm signalling cascade that activates Janus kinases (JAK) and tyrosine phosphorylation of signal transducers and activators of transcription (STAT) proteins. Beside activation of JAK/STAT pathway, MAP/MEK kinase signalling pathway is also activated, leading to ERK phosphorylation and c-fos transcription [48,49].

It is known that histamine can modulate expression of IL-6 receptors on various types of cells like human lymphoid, monocytoid, and hepatoma cell lines. This effect is dependent on specific histamine receptors: whereas activation of histamine H_1-receptors stimulates IL-6 receptor expression, histamine H_2-receptor activation suppresses the expression [31]. Furthermore, activation of histamine H_1-receptor leads to IL-6 production in certain types of cells. The signal is transmitted via phosphorylation of Ca^{2+}-dependent PKC isoforms and activation of two different downstream pathways: c-Raf–MEK–ERK and I kappa B alpha kinase–I kappa B–nuclear factor-kappa B pathway, leading to up-regulation of IL-6 expression [50–53].

We showed that pre-treatment of the cultured astroglial cells by histamine for 24 h significantly amplified IL-6-stimulated NGF secretion from the cells, comparing to the NGF secretion, evoked by either histamine or IL-6 alone [54,55]. The synergistic effect of histamine and IL-6 on NGF secretion might be explained as an outcome of the histamine-stimulated IL-6 receptor expression, or histamine-stimulated IL-6 production, or both, which can only occur after long-term pre-incubation of the cells by histamine.

Amplification of the IL-6-stimulated NGF secretion, reached by pre-treatment of the cells by histamine, is strongly suppressed by histamine H_1-receptor antagonists/inverse agonists (mepyramine and triprolidine). Furthermore, PKC inhibitors (GF 109203X, Go 6976), and MEK1 inhibitor (PD 98059), all effectively block the synergistic effect of histamine and IL-6, but they do not influence significantly the NGF secretion, evoked by IL-6 alone [56].

These results show that stimulation of histamine H_1-receptors and activation of the PKC-MAPK/MEK1 pathway is crucial for amplification of NGF secretion, caused by interaction between histamine and IL-6.

4. Conclusion

Histamine is shown to be a potent stimulator of the NGF synthesis and secretion in cultured astroglial cells and human keratinocytes as well. In both types of the cells the stimulation of NGF production is mediated by the activation of histamine H_1-receptor and transmission of the signal via phosphorylation of Ca^{2+}-dependent PKC alpha isoform and activation of c-Raf–MAPK/MEK1–ERK which in further steps leads to NGF mRNA expression and synthesis of NGF [3,34,38].

The same signalling pathway is involved also in the interactions between histamine, IL-1beta and IL-6, where NGF secretion is amplified (Fig. 2). Whereas histamine and IL-1beta cause additive stimulatory effect on NGF secretion,

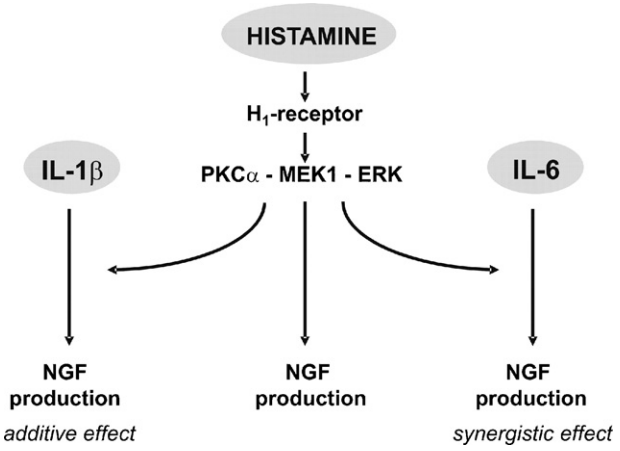

Fig. 2 – Multiple role of histamine H_1-receptor–PKC–MAPK signalling pathway in the stimulation of NGF production. The same signalling pathway is involved in direct stimulation of NGF secretion by histamine, and also in indirect stimulation via different types of interactions between histamine, interleukin-1beta, and interleukin-6, where NGF secretion is amplified.

interaction between histamine and IL-6 causes synergism, which occurs only after long-term pre-incubation of the cells by histamine [47,51,56].

These findings contribute to the clarification of molecular mechanisms, involved in the interactions between histamine, IL-1beta, and IL-6 in the regulation of NGF production. Amplification of histamine stimulation of NGF secretion via histamine–cytokines interactions has important consequences, since NGF may in turn promote histamine release [57–59]. Such a positive feedback loop of histamine/NGF can amplify inflammation response in several inflammatory diseases like allergic dermatitis, atopic dermatitis and asthma, as NGF induces synthesis of immunomodulatory neuropeptides like substance P or calcitonin-gene-related peptide [60], increases the production of inflammatory cytokines or chemokines [61], or enhances the survival or proliferation of neutrophils and T cells [62]. Recent studies show the benefit of histamine H_1-receptor selective antagonist olopatadine, which significantly reduces the increased production of NGF in the treatment of experimentally induced skin inflammation in mice [63,64]. Although the role of histamine H_1-receptor in the effect of olopatadine is not precise yet, histamine H_1-receptor antagonists may have important therapeutic implications in the regulation of histamine-stimulated NGF production and, as a consequence, in the treatment of inflammation, epidermal hyperplasia, and hyperinnervation in certain diseases.

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