Stress-Related Hormones in Drosophila melanogaster

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The response of living beings to adverse conditions, known as the stress reaction, is a complex mechanism including various signaling pathways and hormones. Some are evolutionarily conserved, such as the insulin signaling pathway, others, such as 20-hydroxyecdysone, adipokinetic or juvenile hormones, are taxon-specific in insects. Key components of the neuroendocrine stress reaction in insects are biogenic amines (dopamine and octopamine), juvenile hormone, 20-hydroxyecdysone, adipokinetic hormone and insulin-like peptides.

Keywords: Drosophila melanogaster ; insulin signaling pathway ; juvenile hormone ; 20-hydroxyecdysone ; adipokinetic hormone ; dopamine ; octopamine ; stress

1. Introduction

Adverse environmental effects on living beings launch a series of reactions on the cellular, neuroendocrine and behavioral levels, which leads to the activation of defense processes and enhances adaptation. In insects, the neuroendocrine stress reaction is currently considered to include the following elements: the insulin signaling pathway, biogenic amines, dopamine and octopamine, functioning as both neuromediators and neurohormones, the neuropeptide adipokinetic hormone, as well as 20-hydroxyecdysone and the juvenile hormone–two hormones controlling larvae development, metamorphosis and reproduction. Disruption of any of the components of the neuroendocrine stress reaction can influence insect stress resistance.

2. Insulin/Insulin-Like Growth Factors Signaling Pathway in *Drosophila melanogaster*

The insulin/insulin-like growth factors signaling (IIS) pathway is evolutionarily conserved among all metazoans and performs a vital role in the regulation of growth, development, reproduction, longevity, metabolism and stress resistance [1][2]. In *D. melanogaster*, eight insulin-like peptides (DILP1-8) have been identified: DILP1-5 show significant homology with insulin, DILP6–with insulin-like growth factors, DILP7 and DILP8–with mammalian relaxins [3][4][5][6][7].

DILPs are produced in medial neurosecretory cells or insulin-producing cells (IPCs) of the brain, as well as in the cells of peripheral tissues such as the visceral muscles of the gut, the fat body, which is the main metabolic organ in insects, neurons of the abdominal ganglia, and ovaries in a tissue- and stage-specific way [3][6][8][9][10][11][12]. Neuronal DILPs are secreted into the hemolymph and received by a homolog of the insulin receptor (dInR) for transmitting its signals to target cells [8][13][14][15][16]. DILP7 acts on the Lgr4 receptor bound to G-protein and containing leucine-rich repeats, and DILP8 binds Lgr3 [17][18].

dInR is localized in numerous fly tissues, including the fat body, the endocrine gland *corpus allatum* (*CA*) and follicular cells of the ovaries [19][20][21]. Activation of dInR, directly or through an orthologue of the mammalian insulin receptor substrate (CHICO), launches the kinase cascade, and dAkt/PKB (proteinkinase B homolog) inhibits the transfer of the transcription factor of the *Drosophila* Forkhead box class O family (dFOXO) into the cell nucleus and provokes its return from the nucleus back to the cytoplasm [22]. The main localization of dFOXO in *D. melanogaster* is the fat body of the head and abdomen [23]. dFOXO plays the role of the main regulator of expression of the downstream genes participating in the metabolism, the cell cycle, the stress response, the control of longevity and apoptosis [24][25][26][27]. It has been shown that a mutant dFOXO lacking dAkt phosphorylation sites does not react to IIS inhibition, remains in the nucleus and is constitutively active [28].

3. Stress-Related Hormones in *Drosophila melanogaster*

In *D. melanogaster*, IPCs are similar to vertebrate pancreatic β-cells secreting insulin in response to hyperglycemia, and the role of pancreatic α-cells secreting glucagon in response to hypoglycemia is performed by the cells of the *corpus*

cardiacum (*CC*) gland, which produce a glucagon-like neuropeptide, the adipokinetic hormone (AKH) [3][29][30][31]. Due to the similarity of their functions to those of α- and β-cells, IPCs and *CC*, taken together, are seen as the *Drosophila* analogue of the mammalian pancreatic gland [32].

AKH regulates metabolic response to stress, stimulating catabolic reactions and mobilizing energy stores, especially lipids and trehalose, the latter being the main carbohydrate in insects [33][34]. It has been discovered that AKH deficit leads to obesity and a decrease in the carbohydrate level in *D. melanogaster* imagoes [35][36], and flies with an *Akh* mutation have much lower carbohydrate levels in hemolymph, including trehalose, and are resistant to starvation [34]. It has also been shown that *Akh* expression and AKH content in the cells are under DILP2 regulation in *D. melanogaster* females [11].

The IIS pathway interacts with other key hormones of the insect neuroendocrine stress reaction: 20-hydroxyecdysone (20E) and juvenile hormone (JH), which play a decisive role in growth, development, molting and metamorphosis in larvae, and perform the function of gonadotropins in imagoes, as well as biogenic amines dopamine (DA) and octopamine (OA) [22].

The central location of the OA and DA synthesis is octopamine- and dopaminergic neurons of the brain, the location of the JH synthesis is the *CA* gland [37][38]. It has been established that ecdysteroid biosynthesis during development takes place in the prothoracic gland, and the ovaries serve as the main source of ecdysteroids in imagoes [21][37][39]; seminal glands also contain ecdysteroids, but there is no sufficient evidence of an entire *de novo* biosynthesis pathway in this tissue [39]. In insects, DA and OA play the role of neurotransmitters in the synaptic cleft, neuromodulators within the bounds of one tissue, and neurohormones when being transmitted by the flow of the hemolymph to large distances [40]. It has been shown that they control the activity of the endocrine glands, arousal, desensitization of sensory inputs, various complex behavior forms such as memory and learning, and mobilization of lipids and carbohydrates [40][41][42].

DA is known to participate in JH level regulation, increasing it in young females, and decreasing it in mature ones [43]. Moreover, its regulation has a feedback loop: JH lowers the DA level in young females and increases it in mature ones. DA also regulates the 20E level, increasing it in young females and decreasing it in mature ones; however, no negative relationship has been discovered–20E increases the DA level in young females and decreases it in mature ones. In turn, DA and OA influence the 20E level indirectly through the JH metabolic system. This influence is unidirectional in young females, where it increases the 20E level, and multidirectional in mature ones: OA increases the 20E level, and DA decreases it [43]. Under unfavorable conditions of varying nature, the levels of all these hormones in *Drosophila* imagoes increase sharply (accompanied by a decrease in the activity of their metabolic enzymes), affecting survival, fecundity and longevity [22]. In larvae, stress reaction develops as an inhibition of prothoracicotropic hormone (PTTH) secretion, which leads to a delay in ecdysone secretion and an increase in JH content, resulting in delayed metamorphosis or additional molting and allowing to “wait out” unfavorable conditions [44]. OA and DA levels in larval insects have also been shown to increase under heat stress [44][45].

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