

## NEUROHORMONES IN INSECT STRESS: A REVIEW

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**Abstract** - The neurohormones are the master regulators of all life processes in insects and they create a strategy of stress protecting events. Neurohormones are synthesized mainly in insect brain neurosecretory neurons. Various stressors of different intensity cause specific changes which influence on neurosecretory neurons activity and synthesis of neurohormones (biogene amines, ecdysiotropins, ecdysiostatins, allatoregulatory neurohormones, adipokinetic neurohormones, etc.). Biogene amines in insects may function as neurohormones controlling carbohydrate and lipid metabolism as the primary response of the insects to the effect of stressors. Intermediary metabolism in insects is mainly regulated by adipokinetic hormones which supply organism by energy especially in extreme conditions. Stress induces changes in release of ecdysioregulatory and allatoregulatory neurohormones and modifies ecdysones and juvenile hormones synthesis in prothoracic gland and *corpora allata*. The involvement of hormones of an ecdysteroid or JH type in response to stress creates the danger of an untimely induction of morphogenetic process in target cells. Limiting the quantity of secreted hormones and shortening the period when target cells are sensitive to morphogenetic stimuli removes this danger.

**Key words:** Insects, stress, neurohormones, neurosecretory neurons

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### INTRODUCTION

All living organisms respond to stressful changes of the environment in strikingly various ways. However, with all the diversity of responses to stress at both the cell level and the level of the organism, the major task of all of them is to overcome the effects of the influencing factor and increase the organism resistance. Neurohormones are the master regulators of all life processes in insects and employ a strategy of triggering stress-protective events. Despite the wide differences observed in insects, all life processes are coordinated by only a few neurohormonal compounds which regulate molting hormones (ecdysteroids) and juvenile hormones (JHs, sesquiterpenoids). Neurohormones are synthesized mainly in neurosecretory neurons (NSNs) of the insect's brain and in certain peripheral neurons. Insects are characterized by the presence of specialized NSNs that in the perikaryon synthesize neurohormones which in insects are transported along the axon to the *corpora cardiaca* (CC) and *corpo-*

*ra allata* (CA) and to other neurohemal organs from other ganglia of the nervous chain. From the neurohemal organs, neurohormones are released into the hemolymph. In gross morphology, insect NSNs (and indeed neurosecretory neurons in members of any phylum) are different from other neurons (R a a b e, 1982; O r c h a r d, 1983). Many authors have demonstrated that increase in insects under the influence of a stressor. This synthesis and release of neurosecretory material (NSM) in NSNs release of neurohormones from NSNs can be a normal response of insects to the effect of stressors expressed at the level of the neurosecretory system (A x e l r o d and R e i s i n e, 1984). There have been numerous investigations on the effects of extreme temperatures, trophic unsuitability, insecticides, and other stressors on brain NSNs and other ventromedial neurosecretory cells in the subesophageal ganglion (I v a n o v i ć *et al.* 1975, 1979, 1980, 1985, 1989, 1991; J a n k o v i ć - H l a d n i *et al.* 1983; L e k o v i ć *et al.* 2001; N o r m a n, 1980; P e r i ć - M a t a r u g a *et al.* 2001; P e r i ć - M a t a r u g a

and Lazarević, 2002 a, b; Perić-Mataruga and Lazarević, 2004; Mrdaković *et al.* 2004; Ilijin *et al.* 2004; Nenadović *et al.* 2005; 2006 a,b,c). Various stressors of different intensity cause specific changes (in cation concentration, membrane permeability etc.) which influence synthesis and release of NSM, and histochemical changes in NSNs can be recognized (Janković – Hladni *et al.* 1992; Perić – Mataruga *et al.* 1999; Perić – Mataruga and Lazarević, 2002 a, b; 2003). Many investigations have shown that the response at the level of NSNs in different insect species depends on intensity of the stressor and the duration of exposure (Ivanović *et al.* 1975; Glumac *et al.* 1979; Perić – Mataruga *et al.* 1998; Mrdaković *et al.* 2003).

A stressor signal received by an insect's exteroceptors is transmitted via sensory nerves to the brain, whose neurons (having processed the information and assessed the stimulation level as extreme) transmit a message along cardiac nerves calling for urgent release of neurohormones synthesized in NSNs and stored in the neurohemal organ (CC). The first stress reaction, depending on speed of the metabolic response, is linked with the secretion of biogenic amines (Davenport and Evans, 1994). Under their influence, within a few minutes the reserve energy substrates are mobilized in the fat body within a few minutes. In the next phase of the stress process, a more complex problem of physiological reactions is resolved. Its first stage (provision of energy) is partly realized by neurohormones (adipokinetic neurohormones and hypertrehalosemic factors) in concert with biogenic amines or immediately following their action. At a certain stage in stress development this group of neurohormones is joined by ecdysteroids, which are related to glucocorticoids of vertebrates. The second stage (stimulation of macromolecular synthesis and the associated reparative process) is within the competence of ecdysteroids, whose synthesis is in turn regulated by ecdysiotropic neurohormones. In addition to ecdysiotropins and ecdysio-statins, ecdysteroid secretion in insects can also be modified by juvenile hormone (JH). Neurohormones from the insect brain, allatotropins and allathostatins regulate synthesis of JH. In some cases JH stimulates ecdysteroids secretion and thereby promotes activation of the effector systems subject to its control.

The purpose of the present paper is to give a brief review of the state of knowledge about the main neurohormones involved in insect stress.

## BIOGENIC AMINES

In the central nervous system of both vertebrates and invertebrates, biogenic amines are important neuroactive molecules. Biogenic amines in vertebrates control and regulate various vital functions, including circadian rhythms, endocrine secretion, cardiovascular control, emotions, learning and memory (Hirashima and Morifuza, 1993). In addition to neuropeptides, hormonal activity in NSNs of the insect brain and CC is also manifested by biogenic amines (Stevenson and Spornase-Eichmann, 1995; Perić – Mataruga, 1997; Perić – Mataruga *et al.* 1996), which are similar in their structure and physiological activity to vertebrate adrenaline. In insects, amines like dopamine, tyramine, octopamine, serotonin, and histamine exert their effects by binding to specific membrane proteins that primarily belong to the superfamily of G protein-coupled receptors (Bleau and Bauman, 2001). Study of the role played by biogenic amines in the process of insect stress is a relatively new field. Octopamine is one of the most common biogenic amines in insects. Its presence has been detected in the nervous system, neuroendocrine system, and hemolymph of *Locusta migratoria*, *Schistocerca gregaria*, and other insects (Evans, 1989; Hirashima and Morifuza, 1993). The first experiments showed that in the cockroach *Periplaneta americana*, various stressful factors elicit the increase in glucose (Wilson and Rounds, 1972) and trehalose (Mathews and Downer, 1973) content in the hemolymph. Scientists confirmed that octopamine in the hemolymph of insects can function as a neurohormone controlling carbohydrate and lipid metabolism as the primary response of the insect to the effect of stressors (Downer *et al.* 1984). It was shown that in *P. americana* the hypertrehalosemic factor is influenced by octopamine, and that this factor is released from the octopaminergic neurone via *corpora cardiaca* II (Downer *et al.* 1984). Biogenic amines are assumed to be responsible for stressogenic changes in the energy metabolism of insects (Wilson and Rounds, 1992).

Octopamine can function in the insect hemolymph as a neurohormone controlling short-term lipid and carbohydrate metabolism, being released as a part of the mechanism in response to stressors (Davenport and Evans, 1994). The same authors reported that in *S. firefaria* and *P. americana* mechanical and thermal stressors as well as chemical ones (five types of insecticides) produce an increase in the concentration of biogenic amines.

It was argued that changes in octopamine concentration under the influence of stressors reflect only one of the actions of numerous pharmacological compounds which are freely released under stress conditions. Octopamine functions as a neurohormone which elevates short “energy supply” to muscles for flight or combat in insects (Orc h a r d *et al.* 1982). Stressogenic increased population density in *Mamestra brassicae* and *Nauphoeta cinerea* leads to elevation of octopamine concentration in ganglia of the central nervous system (K o z a n e k *et al.* 1986). Under the stress conditions (high or low temperature, mechanical and chemical stimuli, immobilization, high population density, etc.) the content of biogenic amines (dopamine and octopamine) increases in various insect species (R a u s c h e n b a c h *et al.* 1993; P e r i ć – M a t a r u g a *et al.* 1996; P e r i ć – M a t a r u g a, 1997; G r u n t e n k o *et al.* 2000; H i r a s h i m a *et al.* 2000).

Since the reaction of biogenic amines is extremely rapid (occurring as soon as 10 min after exposure to the stressful factor), the level of dopamine and octopamine increases several times (W o o d r i n g *et al.* 1989; H i r a s h i m a *et al.* 1993). Biogenic amines are known to play an important role in regulation of energy metabolism in insects. Both octopamine and dopamine control glycogen conversion to trehalose and release of the latter into the hemolymph, in addition to which they stimulate glucose and trehalose oxidation and release of lipids from the fat body (O r c h a r d *et al.* 1982 a; W o o d r i n g *et al.* 1989). Changes in the level of biogenic amines caused by unfavorable conditions, as well as the base level of these substances (i.e., under normal conditions), are important for stress adaptation in insects (G r u n t e n k o *et al.* 2004).

Stress-induced increase in JH content is caused by reduced expression of the genes that control enzymes of JH degradation. This is a stress-adaptive event because it leads to a delay in oviposition and makes it possible to “wait out” unfavorable conditions. It is unclear whether the biogenic amines are involved in regulation of JH content under stressful conditions. If so increase in the octopamine level after exposure to different stressors (temperature shock, injury, etc.) should cause a change in the level of JH (R a u s c h e n b a c h *et al.* 1995, 2001, 2002; G r u n t e n k o *et al.* 2000).

## ECDYSIOTROPIC NEUROHORMONES

Ecdysiotropins are neuropeptides that regulate functioning of the prothoracic glands or other ecdysteroid producing cells / tissues. Ecdysteroid biosynthesis in prothoracic glands or ring glands of larval insects is stimulated by neuropeptides called ecdysiotropins or prothoracicotropic neurohormones (PTTH) (B o r o v s k y, 2003; G a d e and G o l d s w o r t h y, 2003).

The structure of PTTH is known from a few insect species, mainly silkworms. They occur in multiple forms, both “large” and “small”. The structure of the “large” PTTH of the silkworm *Bombyx mori* (30 kDa-PTTH or Bommo-PTTH) was elucidated by K a t a o k a *et al.* (1991). The PTTH peptide exists as a homodimer with the two monomers glycosylated and connected by disulfide bonds. The cDNA for “large” PTTH has been cloned and its nucleotide sequence determined (K a w a k a m i *et al.* 1990). Its gene is expressed in only a few neurosecretory cells of the brain (M i z o g u c h i and G i l b e r t, 1994). From data on various characteristics of “large” PTTH (its amino acid sequence, the pattern of its disulfide bonding, its three-dimensional structure, and structure of the gene), it is clear that there is high homology between “large” PTTH and vertebrate growth factors (N o g u t i *et al.* 1995). Vertebrate growth hormone (GH) was detected in NSNs of the protocerebral part of the *Lymantria dispar* L. caterpillar’s brain after exposure to stressogenic conditions (2% quercetin in the caterpillar’s diet) (P e r i ć – M a t a r u g a *et al.* 2004). The mode of action of PTTH has been studied extensively in *B. mori* and *M. sexta*. Experiments performed in vitro demonstrate that signalling of PTTH involves increased  $Ca^{++}$  influx and the presence of inositol trisphosphate (IP3), diacylglycerol (DAG), and/or cAMP (D e d o s and F u g o, 2001; D e d o s and B i r k e n b e i l, 2003). In *M. sexta*, two out of seven (or eight) PTTH-induced proteins have been identified (i.e., b-tubulin and hsp 70). The physiological significance of these proteins for synthesis of ecdysteroids is not known. It has been suggested that PTTH has multiple stress-protective effects on the cell biology of the prothoracic glands, in addition to stimulating ecdysteroidogenesis and protein synthesis (G i l b e r t *et al.* 2000); and that components of the PTTH signal transduction cascade are not fixed, but can change in accordance with stressful living conditions during the development of an insect (R y b c z y n s k i and G i l b e r t, 2003).

The PTTH with a molecular mass of 4–5 kDa is approximately 40% similar in primary sequence to human insulin and is called 4 kDa-PTTH, “small” PTTH, or bombyxin (Iwami, 2000). The genes for 4 kDa-PTTH are predominantly expressed in four pairs of medial NSNs of the brain (Moto *et al.* 1999; Salam *et al.* 2001). In *Samia cynthia ricini* bombyxin genes have been cloned and proven to be expressed in the medial NSNs of the brain (Kimura – Kawakami *et al.* 1992; Yagi *et al.* 1995). Because the structures of vertebrate insulin and bombyxin are similar, it was assumed that bombyxin may play important roles in the sugar metabolism and growth of insects.

What are the stress stimuli that induce the brain to secrete PTTH? It is known that brain NSNs (the source of PTTH) receive their cue through receptor systems, as well as from environmental stimuli such as photoperiod, cold, heat, plant allelochemicals, injury, etc. (Gade and Goldsworthy, 2003; Perić – Mataruga *et al.* 1999; Mizoguchi *et al.* 2001, 2002). Changes in PTTH titers were closely correlated with changes in the circulating ecdysteroid titer, as well as with the occurrence of morphological and behavioral changes that characterize the initiation or progression of metamorphosis or metabolic responses to stress (Gu *et al.* 2000). In addition, stress induced specific changes in the signal transduction of PTTH may also play a critical role in the control of ecdysteroid biosynthesis in the prothoracic glands (Gu *et al.* 2000). A receptor for the 30 kDa-PTTH has not yet been identified.

In *L. migratoria*, *Rhodnius prolixus* and in *Oncopeltus fasciatus* changes in stretching of the intestinal walls serve as a cue for PTTH secretion. It follows that external signals, including those which can be identified as “stimulation”, are able to activate PTTH release or synthesis (Nijhout, 1979). Direct evidence concerning changes in PTTH under the influence of stressors has not been obtained so far. It is generally accepted that ecdysone secretion from prothoracic glands is directly regulated by PTTH. Stress-induced intensification of the prothoracic gland secretory function involves the medial protocerebral NSNs in which PTTH synthesis occurs out (Mizoguchi and Gilbert, 1994). Hence, it is reasonable to consider these observations as an indirect argument in favor of PTTH involvement in the response to stress. More definite evidence for traumatic activation of the prothoracicotropic function of the brain was obtained as a result of microsurgical experiments on *Galler-*

*ia mellonella* caterpillars. In 2- to 3-day-old caterpillars in the final instar, different mechanical damage (cuticle incision, severance of the ventral nerve cord, removal of the imaginal disk) causes precocious molting, and a supernumerary larval instar is formed instead of a pupa. In 4- to 6-day-old caterpillars, the same action delays molting. Transplanting the brain from a 2- to 3-day-old, individual into a 4- to 6-day-old one induces a precocious molt in the latter. The effects of damage on 2- to 3-day-old caterpillars can be reasonably attributed to activation of the cerebral prothoracicotropic function. Under certain conditions, a similar effect is also observed in individuals at the end of their final instar. If in this period caterpillars of *G. mellonella* are deprived of the free space required for cocoon formation, prothoracicotropic activity of the brain is blocked by signals from the outer mechanoreceptors. Surgical damage to the integument restores prothoracicotropic activity of the brain. It should be noted that these two types of stimuli elicit different kinds of response: one of them (limitation of space) delays development, whereas the other (injury) accelerates it. A similar duality of the response to a stressor has been shown to be a peculiar characteristic of the period preceding metamorphosis. Mechanoreceptive signals which inform the organism of environmental conditions unfavorable for pupation prolong the stage of a “wandering larva” and thereby give it additional time to find suitable conditions. More severe damage causes stress-alarm secretion of PTTH and ecdysteroids (Ishizaki, 1989).

Six hours after treatment with formaldehyde vapors, high levels of PTTH-induced ecdysteroid synthesis were found in larvae of *Caliphora vicina*. In the control set, the larvae whose development was delayed by reduced temperature contained practically no ecdysteroids throughout the 48h of the experiment. Chronic intoxication with methanol vapors induced synthesis of a small amount of ecdysteroids already 3 h after the onset of action. At 48 h the titer reached its maximum, yet even then it was much lower than the titer which accompanies *C. vicina* pupariation.

However, it would be wrong to think that stress intensifies PTTH and ecdysteroid secretion in all cases. In particular, a more complex structure of the response to formaldehyde intoxication has been recorded for caterpillars of *B. mori* (Chernysh *et al.* 1998). In intact individuals of the fourth instar, the content of ecdysteroids fluctuated at a low level during the intermolt period; 10 or 12 h prior to the molt onset, the titer rose to a quantity

of 80 ng/g, whereas during the molt it fell to an indefinable value. In damaged caterpillars some hours after the damage, a slight increase over the level in control individuals was observed, but their morphogenetic peak appeared rather blurred, the titer had a maximum value of 40 ng/g, and the molt itself was delayed. In analyzing the effects of damaging actions on dynamics of the preimaginal stage of development, it is easy to detect considerable differences in insect responses. In some cases, damage causes a temporary blocking of morphogenesis, while in others, on the contrary, it accelerates development. Respectively sooner or later than the normal time, PTTH and ecdysteroids are secreted in a morphogenetically effective quantity. It can be assumed on these grounds that the reduction of diapause duration under stress is also due to subthreshold PTTH and ecdysteroid secretion, which is unable to induce morphogenesis immediately. We can thus conclude that developing insects exhibit more various responses to stressor action. Besides peculiarities of the physiological status, qualitative and quantitative characteristics of damage can be a source of variability in the endocrine system's response. It should also be taken into account that every damaging agent, in addition to producing nonspecific stressor effects, induces pathological processes specific to it. In a number of cases these changes may affect PTTH production and steroidogenesis more strongly than the state of stress *per se*. Besides various PTTH-induced morphogenetic disturbances after exposure to stressors, ecdysiotropins play a very important role in metabolic responses to stressors. The small form of PTTH (-bombyxin) has been shown to lower the concentration of the major sugar in the hemolymph (i.e., trehalose) after exposures to stressors and to elevate trehalose activity in the midgut and muscles of larvae of *B. mori*. However, the doses required to be effective were higher than the amounts present in the unstressed larvae (Satake *et al.* 1997). Masumara *et al.* (2000) recently demonstrated that in larvae of *B. mori*, release of bombyxin from the brain into the hemolymph is changed by stress starvation. The titer of glucose in the hemolymph also changes under stress conditions, and a close relationship is observed between changes of glucose concentration and bombyxin titer in the hemolymph. Injection of glucose into starved larvae mimics the effect that refeeding has on the release of bombyxin, suggesting that glucose serves as a signal for inducing the release of this peptide. An insulin receptor homolog has been identified from *D. melanogaster* (Fernandez *et al.* 1995) that shows structural and functional properties similar to those of the insulin tyro-

sine kinase receptors of vertebrates.

Insect ecdysteroids perform a function comparable in some respects to that of vertebrate glucocorticoids. This function is reflected above all in their ability to induce synthesis of certain groups of stress protective enzymes, including microsomal mixed function oxidases, but they probably also change the stress induced activities of enzymes of antioxidative protection (Ropp *et al.* 1986; Perić – Mataruša *et al.* 1997). Ecdysiotropin-induced ecdysteroids (like glucocorticoids) shift metabolism toward the generation of mobile carbohydrate forms, owing to which the pool of utilized energy substrates is replenished (Achrem, 1997).

#### ADIPOKINETIC NEUROHORMONES

Intermediary metabolism in insects is regulated by small neuropeptides of the adipokinetic hormone or red pigment-concentrating hormone (AKH family of RPCH) (Gade *et al.* 1997). Adipokinetic hormones exert a wide range of effects, many of which are analogous to those of vertebrate glucagons (Goldsworth, 1994; Milled *et al.* 1995). Common characteristics of known AKHs are that the peptides have a length of 8–10 amino acids, are amino-terminally blocked by a pyroglutamate residue, and have a carboxy-terminal amide. They contain at least two aromatic amino acids, tryptophan in position 8 and phenylalanine or tyrosine in position 4. Adipokinetic hormones induce increase of hemolymph lipid concentrations in locusts (adipokinetic effect) and increase of hemolymph sugar concentrations in cockroaches (hypertrehalosemic effect). In addition to hyperlipemia and hypertrehalosemia responses, in some dipterans and beetles include inhibition of protein synthesis, activation of glycogen phosphorylase, and inhibition of lipid synthesis (Eibert and Rennwald, 1993). The CC are the main source of these peptides, relatively high quantities of them (in comparison with most other insect neurohormones) are stored in these glands. It has been demonstrated that AKH immunoreactivity is also present throughout the central nervous system of insects (Schooneveld, 1983; Goldsworth *et al.* 1997). Socha (1999) and coworkers have recently shown that AKH after stress exposure can directly act on the insect's central nervous system and thereby stimulate locomotor activity (Orchard *et al.* 1983). Injected extracts from locust CC cause hyperlipemia and alter hemolymph trehalose and lipid concentrations in larvae of *Morimus funereus* (Djordjević *et al.* 1999). The

function of AKH is to provide adequate energy, particularly for the working of wing muscles during stress flight. In the locust, however, hyperlipemia occurs not only during flight, but also as a result of other stressful factors like poisoning with neurotoxic insecticides and plant allelochemicals, unsuitable temperatures, injuries, and starvation (Steele 1985). In the last-named case, however, the rapid and short-term rise of diglyceride concentration is due rather to secretion of biogenic amines, whereas AKH becomes involved at later stages in the response to stress. The fall of trehalose concentration in the hemolymph serves as a cue for AKH secretion in the presence of stressors. Thus, metabolism of lipids appears to be closely associated with that of carbohydrates, which is also controlled by hormones of the CC. Increase in glycogenolysis and the rise of trehalose concentration in the hemolymph are usual components of the response to stress (Socha, 1999). After muscles and other organs have received the additional amounts of lipids and trehalose which they need in stress, the breakdown of reserve energy substrates ceases. It is possible that an important role in the return of metabolism to its normal level is played by hormones antagonistic to AKH and to the trehalosemic factor (Steele, 1985).

#### ALLATOREGULATING NEUROHORMONES

The ability of the CA to synthesize and release JH may be controlled by stimulatory (allatotropic) and inhibitory (allatostatic) neuropeptides that reach the glands via the hemolymph or through nervous connections. To date, only two allatotropins (as compared with several allatostatins) have been isolated from nervous tissues of various insect species belonging to several orders (Elekonič and Horodyski, 2003; Tu *et al.* 2002). These so-called allatoregulating peptides have been bioassayed for their effect on JH biosynthesis. They appear to be widely distributed and occur in non-nervous tissues of insects as well, suggesting that they may also exert physiological action on tissues other than the CA. Allatoregulating neuropeptides have been the subject of several recent reviews in which more extensive bibliographies can be found (Hoffmann *et al.* 1999; Stay, 2000; Gade and Galdsworty, 2003) but information about their role in the response to stress is scarce. Although several allatotropic factors have been identified on the basis of bioassays that demonstrate stimulation of the CA (Gade *et al.* 1997; Gilbert *et al.* 2000; Kou and Chen, 2000; Tu *et al.* 2002; Elekonič and Horodyski, 2003), the primary structure

of only two is known. Allatostatins are structurally diverse peptides and were originally shown (by using a radiochemical assay *in vitro*) to inhibit biosynthesis of JH in the CA of a variety of insects (Hoffmann *et al.* 1999; Gilbert *et al.* 2000; Stay, 2000; Nassel, 2002). Juvenile hormones are a very important group of insect hormones which regulate insect development and the response to stress. The level of JH synthesis is controlled by a complex system of stimulating and inhibiting signals whose relationship varies considerably in different species and living conditions. Neurosecretory material containing allatotropins and allatoinhibins (which possess antagonistic properties) is released via allatal nerves and also from brain NSNs into CA. A peculiarity governing the titer of JH is that both synthesis and the level of metabolic inactivation of the hormone by specific JH-esterases are subject to regulatory influences. The activity of JH-esterases is enhanced by an unknown factor secreted from the brain and from the suboesophageal ganglion in Lepidoptera (Jones, 1995). There are few direct data on the effects of stressors on allatoregulating neurohormones, but the number of indirect indications is fairly great. It is known that stress causes supernumerary molts in the cockroach *Leucophaea maderae*, as well as in *G. mellonella* and *D. melanogaster*. This effect is considered to be associated with prolongation of allatotropic synthesis and CA activity (Mala *et al.* 2005). Stress (amputation of antenna) produces an analogous allatotropic juveniling effect in the *G. mellonella* (Mala *et al.*, 2005). In the butterfly *Choristoneura fumiferana*, both virus infection and treatment with insecticidal hormone analogs lead to the formation of larvoids, which is considered as evidence indicating stimulation of allatotropin and JH synthesis by pathogens or their toxins. An abnormally high JH titer was found in baculovirus-infected *Spodoptera litura* caterpillars (Subrahmanya and Ramakrishna, 1980). Mechanical damage and unsuitable food seem to induce allatotropic brain activity in Lepidoptera. Transplantation of the brain from damaged caterpillars at the beginning of the seventh instar to caterpillars at the end of the instar elicits a supernumerary larval molt in the latter. Temperature shock also alters allatotropin and JH secretion and induces supernumerary molts in caterpillars (Gruntenko *et al.* 2000). The cited facts indicate that physical and biological injuries often cause more intensive or more prolonged allatotropin and JH secretion from CA. The pathological consequences of this response are obvious and find expression in various anomalies of development. Analyzing the dynamics of development and mortality of *D. virilis*

larvae under unfavorable conditions, Rauschena-bach *et al.* (2001) conclude that the principal cause of mortality is blocking of the pupariation process due to inhibition PTTH and ecdysteroid secretion. An adaptive advantage was on the side of those individuals in which, under the given conditions, the gene activator of JH esterase was not expressed. Such individuals were able to overcome the critical stage of ontogenesis owing to preservation in the hemolymph of a JH titer sufficient for prothoracic gland activation (Rauschena-bach, 2001). Within the framework of this hypothesis, the leading role is attributed not to increase of JH secretion, but rather to blocking of its metabolic degradation (by a JH esterase-regulating factor from the brain), but the result proves to be the same as during stressor activation of CA. It should be noted that the JH-protective effect in this case is mediated by ecdysteroids. This fact emphasizes the interrelation of separate elements of a common mechanism of adaptation. In the intermolt period, the effect of JH may contribute to increase of cell resistance due to activation of ecdysone-dependent macro molecular synthesis. Owing to this or resulting from direct action on the enzyme and immunological protective systems, introduction of JH analogs induces the main catatoxic system (i.e., microsomal mixed-function oxidases) in the housefly *Musca domestica* and suppresses development of the nucleopolyhedrosis virus in caterpillars of *Hyphantria cunea* (Boucias and Nordin, 1980). Stimulation of JH synthesis or delay of JH degradation may cause a rise of stress resistance in a different way as well. It is known that high allatostimulating activities and a high JH titer under stress conditions often promotes the onset of larval diapause in some Lepidoptera species. In such cases, stress-induced intensification or prolongation of JH secretion may cause the state of diapause (Chernysh and Simonenko, 1998). The chain of such facts logically leads to the idea that in insects with the above type of diapause regulation a stress-induced rise of the JH titer under certain conditions switches on a mechanism of passive defense against damage associated with temporary blocking of growth, morphogenetic transformations, or reproduction. Activity of the brain was measured as the incidence of supernumerary molts by 1-day-old specimens of the last instar of *Galleria* larvae (recipient) implanted with brain dissected from either cooled or control larvae. Implantation of one brain taken from a donor on the second day after chilling results in about 50% occurrence of supernumerary molts (Rauschena-bach *et al.* 2001). The brain taken from an unchilled donor and implanted into a larva of the same age produces about

20% occurrence of supernumerary molts. Activity of the brain taken from chilled larvae changes with passage of time after chilling. Implantation of brains dissected at the end of a 3-h chilling period results in about 20% occurrence of supernumerary molts, while brains taken 18 h after cooling stimulate about 60% of recipients to produce supernumerary molts. The brain still has very high allatotrophic activity 24 h after chilling; it then declines, and 48 h after chilling stress application there is no difference between chilled and unchilled larvae. On the second and third day after chilling, activity of the brain decreased to the level observed just after chilling (Cannon and Black, 1988). The same chilling stress (3 h at 0°C) has different effects on brain allatotrophic activity, depending on the age of cooled larvae. Brains of freshly molted last instar larvae have the highest allatotrophic activity, but in this case chilling causes a very high mortality rate (about 80%). Activity then declines slightly, but is still about two times higher than in brains of the same age of unchilled larvae. In further experiments it was shown that an implanted brain must be present in the host larva for at least 2 days in order to induce supernumerary moltings, but even then it has no effect on the activity of the host brain (Cannon and Black, 1988).

## CONCLUSION

All life processes (including the response to stressors in insects) are mainly regulated and coordinated by only a few hormonal compounds, viz., neurohormones, ecdysteroids, and juvenile hormones. In some cases, the same neurohormonal signal has different effects on insects, depending on which stage of the life cycle the insect is in and on the duration and type of the stressor effect. The metabolic response of insects to stress is linked with brain secretion of biogenic amines. In the course of a few minutes after the influence of stressors, reserve energy substrates are mobilized from the fat body. In a later phase of the response to stress, provision of energy is partly realized by adipokinetic neurohormone and/or hypertrehalosemic factors in concert with biogenic amines or immediately following their action. At that stage in development of the response to stress, this group of hormones is joined by steroids related to glucocorticoids of vertebrates (ecdysteroidogenesis in insects is regulated by prothoracicotrophic neurohormones). Survival under extreme conditions is most closely associated with maintenance of an intermediate ecdysteroid titer which surpasses the basal level characteristic of intact individuals during the intermolt period, but does not attain morpho-

genetically significant values. Thus, bringing ecdysteroid secretion into line with the needs of a damaged organism is a task more complex than in the case of other hormones. The simplest and most reliable way of resolving this problem would be through the existence of two forms of PTTH, one of which induces high morphogenetic activity of the prothoracic glands, while the other ensures a moderate level of protective metabolic activity. Secretion of PTTH and ecdysteroids can be modified by JH. In some cases, JH stimulates ecdysteroid secretion. The involvement of hormones of an ecdysteroid or JH type in response to stress creates the danger of untimely induction of morphogenetic processes in target cells. Limiting the quantity of secreted hormones and shortening the period when target cells are sensitive to morphogenetic stimuli remove this danger.

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## НЕУРОХОРМОНИ У СТРЕСУ КОД ИНСЕКАТА

ВЕСНА ПЕРИЋ-МАТАРУГА, ВЕРА НЕНАДОВИЋ, и ЈЕЛИСАВЕТА ИВАНОВИЋ

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Неурохормони регулишу све животне процесе инсеката и креирају стратегију одговора организма на деловање стресора. Неурохормони се у највећој мери синтетишу у неуросекретним неуронима протоцеребралног региона мозга инсеката. Стресори различитих особина и интензитета специфично мењају активност неуросекретних неурона и синтезу неурохормона (биогених амина, егдизотропина, егдизостатина, алаторегулаторних неурохормона, адипокинетичких неурохормона итд.). Биогени амини имају улогу у контроли метаболизма угљених хидрата и липида у почетним фазама стресног одговора инсеката. Интермедијерни метаболизам је регулисан добрим делом адипокинетичким неурохормонима који учест-

вују у обезбеђивању довољне количине енергије која је потребна за превазилажење екстремних услова. Стрес изазива промене у лучењу егдизорегулаторних и алаторегулаторних неурохормона и модификује интензитет синтезе егдизона и јувенилних хормона у проторакалној жлезди и *corpora allata*. Промене у количини егдизона и јувенилног хормона у стресу повећавају ризик почетка временски неадекватних морфогенетских промена у ткивима инсеката. Стресом изазване промене у количини морфогенетских неурохормона су ограничене а и периоди осетљивости ћелија на морфогенетске стимулусе се мењају у стресу ограничавајући донекле могућност неадекватних морфогенетских промена.