The basis of the stress reaction

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The ubiquitous presence of stressful stimuli makes stress one of the most important causes of physiological or pathophysiological changes in an organism during its entire lifespan. The stressors can be divided (according to their nature) into physical, chemical, psychological, social and disturbing cardiovascular/metabolic homeostasis effects, which can affect multiple systems. Here we emphasize that although stress is classified according to its nature, multiple mechanisms are affected. We will focus on mechanisms of stress reaction with the aim of maximal brevity. The pathways that are activated in response to stressful stimuli with respect to specific types of stressors are described. The central processing of a stress response comprises central aminergic neurons, noncatecholaminergic brainstem neurons, hypothalamic nuclei and structures of the limbic system. As a response, specific efferent pathways are activated. Special attention is given to stress effects in the central nervous system and vital functions (heart function and respiration).

Keywords: Afferent and efferent stress pathways, allostasis, stress reaction, stressors.

THE ubiquitous presence of stressful stimuli makes stress one of the most important causes of physiological or pathophysiological changes in an organism during its entire lifespan. Here we emphasize that although stress is classified according to its nature, multiple mechanisms are affected. We will focus on mechanisms of stress reaction.

Stress

The term 'stress', introduced to life sciences in the 1930s by Hans Seley[1], is now overused by many people, especially by those who do not understand what it really means. On the other hand, an accurate definition of stress is not available as yet. In addition, as Seley noted, the term was not appropriately selected due to his inadequate English. He later claimed that he should have called it 'strain syndrome'.

Definitions of stress

It is not surprising that there are many definitions of stress. One of the usually accepted definitions mentions that stress is a physical, mental, or emotional response to events that cause bodily or mental tension. Another definition of stress was provided by Goldstein[2]: a condition where expectations, whether genetically programmed, established by prior learning, or deduced from circumstances, do not match the current or anticipated perceptions of the internal or external environment; this discrepancy between what is observed or sensed and what is expected or programmed elicits patterned, compensatory responses. In extreme understanding, stress can be anything that contributes to virtually any disease in humans[3]. In our view, stress is the body's response to strain (inner or outer). This response is characterized by stress response elements that could have both positive impact (eustress)[4] or a negative impact (distress)[5] on the body. As this definition is short, it needs some explanation of terms that are given in Table 1. Shortly before his death, Seley[6] precisely defined mistakes usually connected with stress. There are important facts that should be mentioned, as many people misinterpret stress or associate erroneous meanings about it. It is necessary to emphasize that stress is not nervous tension[6], as it can occur in lower animals and even in plants[7] which have no nervous systems.

Further, Seley[6] pointed out other facts. It is necessary to consider hormone response in addition to nervous response. Stress is not only the release of 'emergency' hormones from the adrenal medulla. It is necessary to comprehend it as a more complex reaction. Stress is not the sole cause of adrenocortical hormone secretion (there are other regulations via the hypothalamus–pituitary–adrenocortical (HPA) gland axis); it is not only the nonspecific result[3] of harmful events. Normal and/or enjoyable movements (computer games, successfully leading a company, lovemaking) are able to activate stress response elements without eliciting damage (see the term 'eustress' in Table 1). The alarm reaction is not caused by stress (the cause is the stressor, not the stress itself), and stress is not identical to the alarm reaction. Later, Seley[6] also corrected his previous opinion that stress is a nonspecific reaction. On the other hand, stress is not a reaction to a specific thing. It should be considered as a reaction that helps the organism cope with different situations and, therefore, stress cannot and should not be avoided.

Time context of stress reaction

In respect of duration, the stressors can influence the organism: (i) acutely (i.e. acute/single intermittent stress),

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Table 1. The explanation of terms used in the text

Stress response elements	Stress reaction is characterized by the pathways that are evoked by stressor. First, Seley hypothesized that stress reaction is non-specific. Now, the responses to stressors are considered as specific. Therefore, every response that consists of part of some specific pathway could be understood as stress response element. The main stress response elements are: specific activation of prefrontal/orbitofrontal cortex and limbic system, NTZS activity, activation of catecholaminergic groups in brainstem/medulla oblongata, activation of HPA axis and adrenal gland.
Eustress	The stress situation helps the organism to cope with strain. In that way stress may have an adaptive and motivational role. The positive, 'good' stress is called eustress. This type of stress is connected with the stress response elements as well as with desirable events in a life.
Distress	The opposite term to the eustress, ' bad' stress. When individual can not adapt to the stressful stimuli, then the distress occur.
Homeostasis	Coordinated physiological processes which maintain most of steady states in the organism.
Allostasis	The ability to maintain stability through change. Upon exposure to stressor, physiological responses are initiated, leading to allostatic responses. If allostatic responses are efficient, the organism adapts. When adaptation is not successful the allostatic load results in damage to various organs.
GABA	Gamma-amino butyric acid (main inhibitory neurotransmitter).
NO	Nitric oxide.
NTS	Nucleus tractus solitrarii.

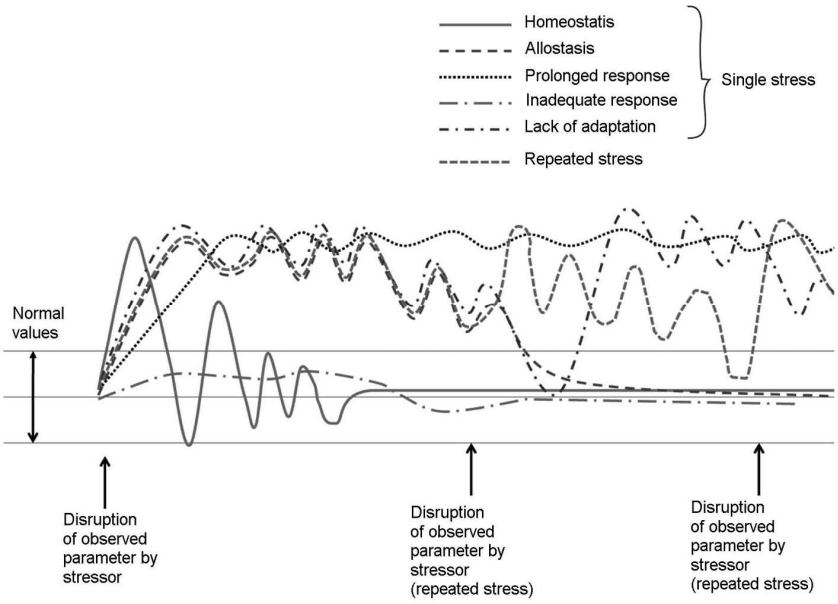

Figure 1. Homeostatic and allostatic mechanisms. Homeostasis (continuous line) represents the situation when the system reacts to disruption by a tendency to correct the values on set-point as soon as possible. Allostasis (dashed line) is adaptation through another 'set-point'. If this adaptation is not adequate, the allostatic load occurs. There can be prolonged response (dotted line), inadequate response (dotted-and-dashed line) or lack of adaptation (short dotted-and-dashed line). Maladaptation can also be the result of repeated disruption of homeostasis (long dotted line). Adapted from McEwen[9].

or (ii) chronically/repeatedly (i.e. chronic/repeated/long-lasting stress).

The repeated influence of a stressor can have great significance in the context of allostasis, which is defined[8,9] as the ability to maintain stability through change (Figure 1). Allostasis is an essential component of maintaining homeostasis. This process is connected to the active process of adaptation. Upon exposure to a chronic stressful situation, physiological responses are initiated, leading to allostatic (adaptive) responses, which are comprised of systems similar to the stress effector systems. If allostatic responses are efficient, the organism adapts and is protected from damage. In other cases, when adaptation is not successful (responses are prolonged or inadequate, the organism is overstimulated, or a lack of adaptation occurs), the allostatic load results in maladaptation and damages various organs[10].

In contrast to homeostatic mechanisms, allostatic regulations are not dependent on set-point mechanisms, and anticipation of the need is an important element. Allostatic load reflects lifestyle (e.g. eating a high-fat diet, lack of exercise, etc.) and disturbances in diurnal rhythm (e.g. sleep deprivation) that lead to overexposure of various tissues to stress mediators.

Although allostasis is the event that maintains homeostasis, we would like to emphasize that this is an active process of adaptation that maintains the existence of an individual by change. Allostasis describes mechanisms that change the controlled variable by predicting what level will be needed and then overriding local feedback to

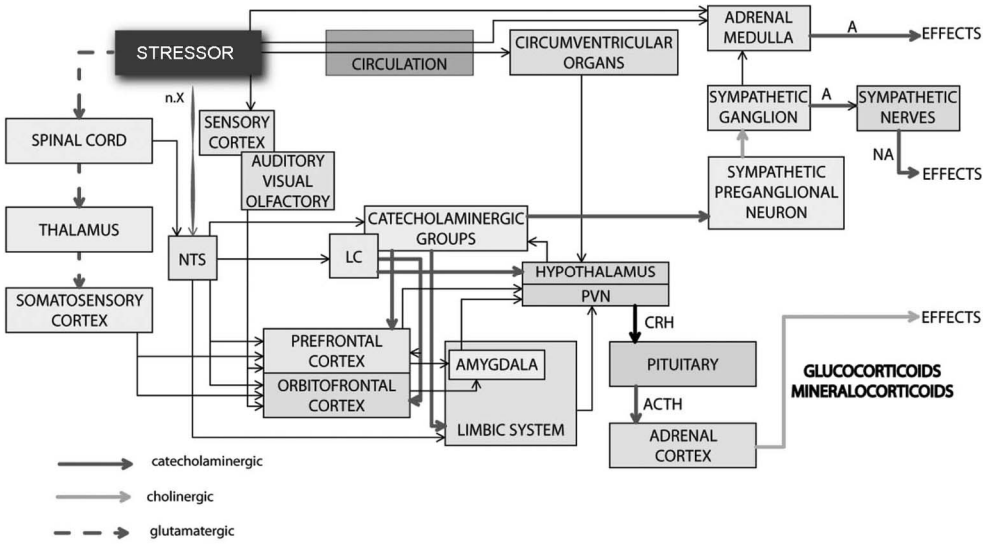

Figure 2. Schematic diagram of stress pathways activation, processing of stress response in the central nervous system and the effector pathway of stress response. Not all the pathway are shown. NTS, Nucleus tractus solitarii; LC, Locus coeruleus; NA, Noradrenaline; A, Adrenaline; CRH, Corticotropine releasing hormone; ACTH, Adrenocorticotropine hormone. Adapted from Kvetnansky *et al.*[39], with changes. Arrows indicate type of involved transmitter: full black line, catecholamines; dashed line, glutamate/aspartate; full gray line, acetylcholine. See text for details on afferent and efferent pathways and central processing of stress response.

meet anticipated demand[11] (Figure 1). While homeostasis tends to correct the changed parameter to initial values, allostasis represents the situation when another set-point is established and is an adequate reaction to a stressor. Allostatic load leads to failure of adequate response (Figure 1); then, prolonged response to stimuli, lack of adaptation and inadequate response can occur. Allostatic load also occurs in the presence of too much stress.

The concept of stress reaction

Simply stated, stress represents the situation in which an organism is affected by a stimulus (i.e. the stressor). This event evokes changes in the organism that lead to changes in the output system (this involves two major routes: neuronal and neuroendocrine; Figure 2). Therefore, it is also possible to consider stress as a reflex reaction/behaviour in which the afferent pathways are represented by stressor activation of receptor(s). The centre is a complicated network (relationship) of the specific areas of central nervous system (CNS) mechanisms (involving emotional/neuroendocrine/neuronal integration). Finally, the effectors (efferent pathways) are represented by systems activated in order to optimize the organism's reaction. All processes are simplified in Figure 2.

Stressors

Usually stressors are stimuli that elicit stress reactions. Generally, the most frequent stressors differ in experimental animals and human beings. Stressors can be divided according to their nature (see Figure 3): (i) Physical, (ii) chemical, (iii) psychological, (iv) social, (v) disturbing cardiovascular/metabolic homeostasis and (vi) affecting multiple systems.

There is no stressor that impacts the organism by only one mode of action (Figure 3). In animal research, the stressors used are mixed, and they affect multiple systems. This is an important fact that should be kept in mind when studying stress. Despite this, evidence that the responses of organisms to various stressors are different is increasing[3]. In humans, the stressors that are most frequent differ from those usually used in animal research. Majority of stressors are psychological and social (see, for example, the list of the most important life stressors as described by Miller and Rahe[12]). These stressors then as second effect cardiovascular/metabolic/immune processes in the body (i.e. by elevated catecholamines, glucocorticoids, etc.). Of course, it is necessary to emphasize that stressors can differ in the developing countries, and physical and chemical stressors are more frequent in animals than in humans[13]. Typically, the animal encounters an infection (i.e. chemical stressor) from a predator/aggressor of another animal strain (i.e. physical and chemical stressors that also have psychological consequences), aggressive animals of the same strain (i.e. physical, chemical and psychological stressors), or haemorrhage, exercise, forced swimming, food/water deprivation and pain, which are usually the stressors that affect multiple systems.

Afferent pathways of stress reaction

The afferent stress pathways correspond to the activated systems, i.e. cold, heat and vibrations have specific receptors in the skin: the projections comprise of the

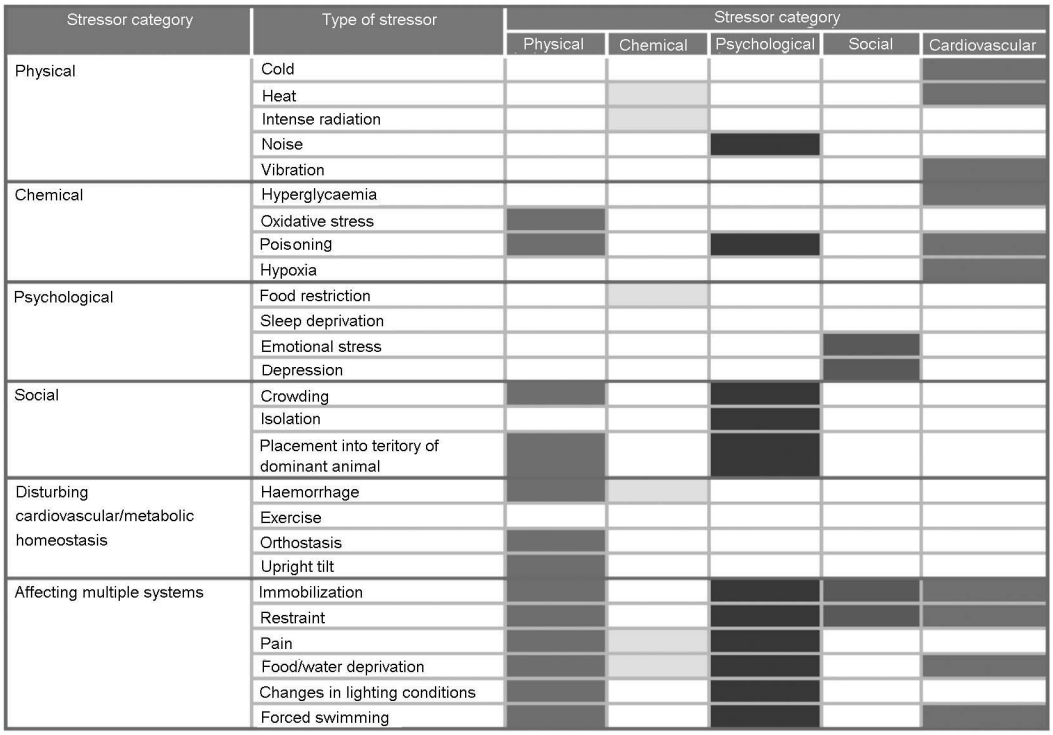

Figure 3. Types of stressors. Not all types of stressors are mentioned. The impact of stressor is shown by different shades of grey. In case of stressors affecting multiple systems, the respective targets are shown. Similarly, if the stressor impact is not by only one mode of action (but mainly), the other modes of action (minor) are also shown. It can be deduced from the figure that there is no stressor effecting the organism by unique way.

sensitive pathways, are processed in the thalamus and then conducted to specific brain regions. These pathways may comprise of different nerves (cranial, viscerosensitive and somatosensitive); neuronal pathways are not the only ones are activated by stressors. Especially chemical signals (such as hypoglycaemia, hypoxia, oxidative stress, poisoning and changes in osmolarity) could affect receptors (and thus activate neuronal pathways that send information about stress) and humoral pathways. These signals enter the CNS via circumventricular organs[3,14]. These pathways do not work as 'soloists', but the stress projection is in accord with neuronal activation.

The humoral signals can affect the CNS in multiple pathways: (i) when the molecule is lipophilic, it can pass freely through the blood–brain barrier; (ii) via circumventricular organs[14], and (iii) by activation of transduction mechanisms on blood vessels that release chemical signals to the brain[15].

In addition, another way to transform chemical signals into neuronal signalling is via the sensitive function of the adrenal gland (medulla). This tissue is rich in viscerosensitive neurons (vagal and spinal), and thus can serve as a sensor[16]. Specifically, examples that illustrate the neuronal afferent stress pathways are shown in Figure 2.

Physical stressors: (i) Cold and heat – These activate peripheral thermoreceptors (warm and cold receptors[17]) located in the skin (on free nerve endings Aδ and C). There are more cold than heat thermoreceptors in the skin, majority of which express TRPV (transient receptor potential vanilloid) channels (for details, see Nakamura[17]). In addition to peripheral cold and heat receptors, the reaction to these stressors is also connected with the activation of central thermoreceptors (in the hypothalamus). When the temperature rises to 45°C, nociceptors are activated. Cold receptors react at temperatures between 25°C and 35°C, and heat receptors react at temperatures between 38°C and 48°C (ref. 18). The information from receptors is led via specific nerve pathways into the spinal medulla. The information passes to neurons in the Rexed laminae III–V (the neurotransmitters are usually excitatory amino acids, i.e. glutamate or aspartate), where it is connected to spinothalamic neurons in the anterolateral system (tr. spinothalamicus, tr. spinoreticularis and tr. spinotectalis). The important part of the pathway is collateral from the reticular formation to the substatia grisea (pain stimuli; substatia grisea is one of the important inner analgesic systems releasing opioids and thus, moderates pain). The information is then led from the thalamus to the somatosensory cortex in the brain.

(ii) Noise – As can be deduced from Figure 3, noise affects the organism not only physically (activating the hearing response), but also psychologically. In that context noise is considered as uninterrupted activation of the auditory pathway. Alternatively, if noise exceeds the intensity of 10 W m^{-2}, it is perceived as pain (see below). The auditory pathway begins with hairy cells (receptors)

that lead the information to the spiral ganglion neurons (SGN)[19]. The transduction mechanism between the hairy cells and the dendrite of the spiral ganglion neurons comprises of glutamate and/or aspartate. Axons of the SGN terminate at the cochlear nuclei, and the synapse is again glutamatergic. Three pathways (corpus trapezoideum, stria acustica intermedian and stria acustica dorsalis) connect the cochlear nuclei and the next structure in the auditory pathway – the olivar nuclei (again, a glutamatergic synapse). The olivar nuclei afferentate to the colliculus inferior (excitatory acids synapse), which passes the information to the corpus geniculatum mediale (although the main neurotransmitter is glutamate, NO and GABA also play important roles), and then the signal finally reaches the auditory cortex (Brodmann area 41 and 42). Here, the main mediators are GABA and glutamate; in secondary cortex structures, the main mediator is NO.

Chemical stressors: (i) Hypoglycaemia – This affects viscerosensitive activity of the vagus nerve (there are glucoreceptors on the endings). The signals are transduced to ncl. tractus solitarii (NTS) and then to other brain structures[20]. In addition, hypothalamic glucosensitive neurons are activated. Lack of glucose in the hypothalamus leads to activation of orexigenic neurons (mainly in ncl. arcuatus), producing neuropeptide Y, agouti-related peptides, hypocretins/orexines, melanin concentrating hormones, galanin, dynorphyin, β-endorphin, GABA, noradrenaline and adrenaline[21]. When a low lipid reserve in adipose tissue is present, blood leptin levels fall and activate the ncl. arcuatus in the hypothalamus. The activation of orexigenic neurons in the hypothalamus leads to decreased energy expenditure and encourages target-oriented behaviour (attempts to find food).

(ii) Poisoning – This is usually comprehended as a single stressor, but there are many poisons (snake/bee/wasp venom, toxins (bacterial, mycotoxins, and toxins from marine animals) and artificial poisons (organophosphates, which is one of the most common causes of poisoning worldwide)). Every form of these poisons elicits specific reactions that activate one or more pathways leading to activation of stress response elements. As an example, organophosphates are inhibitors of acetylcholinesterase[22], the enzyme that cleaves acetylcholine to acetate and choline. Inhibition of this enzyme leads to an increase in the acetylcholine level[23], massive activation of nicotinic receptors in the neuromuscular junction[24], and the activation of somatosensory neurons (and sometimes pain mechanisms) as a result of permanently contracted muscles. In addition, acetylcholine levels increase in parasympatho-smooth muscle varicosities (there are muscarinic receptors), which can lead to the activation of viscerosensitive neurons (as a result of permanently contracted muscles). An increase in acetylcholine levels can directly activate muscarinic and nicotinic receptors in the CNS and affect different CNS-regulated events such as synaptic plasticity[25], cognitive processes[26,27], motor coordination[28], attention, circadian rhythms[29], food reinforcement, drug addiction[30] and depressive-like behaviour[31]. Finally, visceral organs are under the control of the autonomous nervous system. Therefore, the heart can be affected in terms of heart rate (decrease), contractility (decrease), conduction (decrease) and threshold of activation (increase), and the symptoms of cholinergic hyperactivation (salivation, increased gastrointestinal motility, etc.) can occur.

(iii) Hypoxia – Both peripheral and central receptors monitor oxygen saturation. Carotid body (glomus caroticus) cells record the partial oxygen pressure[32], and then the signals are transduced to the brain via the vagal and glossopharyngeal nerves. In addition, blood oxygen partial pressure is monitored by brainstem cells[33]. Hypoxia also affects the cardiovascular system. In an effort to supply oxygen to tissues, the heart rate increases, the vessel diameter decreases, and so on.

Psychological stressors: Sight, smell, taste, sound and statokinetic signals are led via specific pathways in the visual, auditory, olfactory and taste senses, and the vestibulary cortex. In the cortical structures, the signals are processed and the stress response elements are activated. It is important to note that concrete stimuli are not only able to elicit a stress response, but also can induce visions, thoughts, fantasies and words (i.e. stress can be discussed). Food restriction activates the same pathways as discussed in the case of chemical stressors above and emotional stress is connected with activation of emotional circuits (the hypothalamus, amygdala, limbic cortex, septum and hippocampus).

Social stressors: These stressors can activate similar pathways as psychological stressors (visual, olfactory and acoustic). In addition, the other pathways (heat, cold, tactile and pain) can be activated. For example, the placement of an animal (or a human) in the territory of a dominant animal (person) can be connected with pain, cold (the animals usually stay close each other), and haemorrhage. Similar to psychological stress, social stress can be affected by other CNS structures such as the hippocampus[34].

Disturbing cardiovascular/metabolic homeostasis: Haemorrhage – Volumoreceptors and baroreceptors in the heart and vessels are activated by changes in blood volume. The decrease in volume is lead via viscerosensitive neurons of the nervus vagus to the ncl. tractus solitarii. In addition, changes in osmolarity (and water deprivation) are able to activate specific hypothalamic nuclei (ncl. supraopticus and ncl. paraventricularis). The decrease in blood volume also affects thermoregulation,

as blood is an important medium of thermodistribution in the body and changes the concentration of electrolytes and other substances in the blood.

Affecting multiple systems: (i) Pain – This is transduced via specific nociceptors[35]; the first neuron ends in the dorsal horn of the spinal medulla (Rexed laminae I. or V.)[36]. Then, the signal is lead into the thalamus and specific brain regions (postcentral and cingular gyrus). Molecular transmission mechanisms of pain signals are not fully understood, but there several molecules ('inflammatory soup'[36]) that are able to evoke activation of nociceptors (actylcholine, histamine, catecholamines, bradykinine, substance P, serotonine, prostaglandine E1 and E2, ATP, some ions (K^+, Na^+, H^+), leukotriens, phospholipids, etc.). Visceral and somatic nociceptive neurons release substance P and excitatory amino acids (target: NMDA receptors). Substantia grisea is, as has been stated earlier, opioidergic. These neurons are an important part of the so-called stress analgesia (during acute stress, the pain transduction is inhibited in order to strengthen the escape/attack reaction). The thalamocortical pathway is glutamatergic. Importantly, pain is also connected with emotional stress. The spinomesecephalic tract leads the information from spinal neurons to the ventromedial hypothalamus, and the spino-parabrachio-amygdalar tract targets the information to the amygdala. Then, emotional circuits are activated.

(ii) Food/water deprivation – In simple terms (or as one part of the reaction), food deprivation leads to hypoglycaemia. Water deprivation (via the subfornical organ) affects osmoreceptors in the hypothalamus[14], which activates the mechanisms leading to decreased water use (via activation of the paraventricular nucleus) and activates the release of an antidiuretic hormone (ADH), which leads to an increased reabsorption of water in the kidneys. At the same time, thirst and water-seeking behaviour starts.

Central processing of stressful stimuli

Central processing of stressful stimuli comprises of many brain circuits that are activated specifically by precise stressors. In addition, in central processing (described below), stressful stimuli activate structures involved in memory processing, such as the hippocampus[34], and reward structures such as the ventral striatum[37] and the cerebellum[38]. This helps the organism to cope with stress.

According to Pacak and Palkovits[3], the neuronal circuits activated in response to stressors can be divided into the following. (a) short circuits (also called spinal stress responses, which are based on spinal reflexes), and (b) long circuits (also called supraspinal stress responses and include higher centres; see below).

The central structures are central aminergic neurons (catecholaminergic neurons and serotonergic neurons), noncatecholaminergic brainstem neurons (brainstem neurons and neurons of the nucleus tractus solitarii (NTS)), hypothalamic nuclei and structures of the limbic system[3] (Figure 2). In addition, danger pathways, circumventricular organ neurons and neurons of the nucleus interstitialis striae terminalis also participate in the processing of stress by the CNS. The role of these structures are described below.

Central aminergic neurons: The CNS releases several neurotransmitters at the synapses, and the neurons that synthesize specific neurotransmitters form nuclei named specifically according to the neurotransmitter. Thus, nuclei can be divided into catecholaminergic (designated A: A1–A7 as noradrenergic and A8–A17 as dopaminergic; as well as C: C1–C3 as adrenergic), serotoninergic (designated B: B1–B9), cholinergic (CH1–CH6) and others (histaminergic, glutamatergic, etc.) that are not as important regarding stress in the CNS.

(i) Central catecholaminergic neurons – The role of dopaminergic neurons in the processing of stress responses is controversial[3]. As stated above, the first group of neurons can produce noradrenaline (A1–A7, ventrolateral and the dorsomedial medulla oblongata). These neurons project to the hypothalamus and the limbic system. The neurons of the main catecholaminergic nucleus (locus coeruleus) are also noradrenergic and contribute to the central organization of the stress response. The axons of A1 group cells (located from the level of the medulla–spinal cord junction up to the level of the area postrema) project to the forebrain and innervate mainly hypothalamic and limbic structures[39]. The highest density of noradrenergic terminals is found in the parvocellular subdivision of the paraventricular nucleus (PVN) that contains majority of CRH (corticotropin releasing hormone)-synthesizing neurons. A2 group cells (dorsomedial medulla, partly in the NTS) project to the neuroendocrine hypothalamus[39]. Locus coeruleus neurons (A6, responsible for passing the stress signals to the forebrain and organization of stress responses[40]) respond to different stressful stimuli and project to the cerebellum and to the basal ganglia[39]. In addition, some projections end in the hypothalamus, limbic system and the spinal cord. A5 and A7 noradrenergic cell groups are located in the ventrolateral and lateral pons respectively.

Their neurons project to the spinal cord with special high terminal density to the sympathetic preganglionic neurons in the intermediolateral cell column and to the sensory projecting neurons in the dorsal horn. A5 neurons receive direct neuronal input from the PVN. The second group of neurons synthesizes adrenaline (C1–C3). Adrenergic neurons are present in the middle portion of the ventrolateral medulla (between the A1 and A5 cell groups, rostrocaudally). C1 group neurons project to the endocrine hypothalamus and the spinal cord, where there

are innervate sympathetic preganglionic neurons in the intermediolateral cell column. C2 cell group (dorsomedial medulla) axons join the ventral noradrenergic bundle and participate in the adrenergic innervation of the hypothalamus and the limbic system.

(ii) Serotonergic neurons – The main serotoninergic neurons are localized in ncl. raphe (the lower part of brainstem, B1–B6). The projections target the hypothalamus, the limbic structure (rostral parts) and the pituitary gland (dorsomedial parts). The spinal cord also receives projections from these neurons. Serotoninergic rapheal neurons specifically react to restraint, cold, pain and, especially, immobilization stress[3].

Non-catecholaminergic brainstem neurons: These neurons are localized in the ncl. parabrachialis. The lateral part of this nucleus transmits information from the NTS to the forebrain. Non-catecholaminergic neurons surrounding aqueducts are an important part of antinociceptive behaviour and autonomous reactions. These neurons respond specifically to multiple stressors.

(i) Brainstem neurons – The main groups of neurons responding to the stressful stimuli are pre-motoric sympathetic neurons (cholinergic), parasympathetic preganglionic neurons (cholinergic) and medulla oblongata structures that transmit the signal to other brainstem neurons (ncl. raphe, ncl. Kölliker-Fuse and ncl. parabrachialis lateralis; see above) and the hypothalamus (ncl. paraventricularis). These neurons respond specifically to a haemorrhage, respiratory distress, visceral, or somatic pain or inflammation.

(ii) Neurons of the NTS – The NTS receives a huge spectrum of signals, mainly visceral, and less somatic (i.e. gastrointestinal, cardiovascular and respiratory), but also nociceptive, and transmits these to higher structures[3]. The target structures are autonomic centres regulating cardiovascular, respiratory and behavioural functions. There is also efferentation to the insular cortex, which helps maintain food intake, visceral memory processes, reward behaviour and autonomous reactions. The NTS is part of the dorsal vagal complex (DVC), which is able to monitor chemical signals from blood and cerebrospinal fluid. As a part of the vagal nerves, the efferentation from the NTS also coordinates the function of the HPA axis during stress reactions.

Hypothalamic nuclei: The hypothalamus is one of the most important integrative centres in the brain[17,41–43]. It consists of a several nuclei (more than 20), and almost all participate in the stress reaction[3]. The paraventricular, arcuate and medial preoptic nuclei project to both the median eminence (neurohumoral output) and brainstem/spinal cord autonomic centres (neuronal output). Descending fibres may terminate on autonomic preganglionic neurons directly or indirectly through brainstem (A5) catecholaminergic neurons. Stress-responsive neurons are also present in the nuclei that have majority of intrahypothalamic projections (ventromedial, dorsomedial, perifornical and supramamillary nuclei). Paraventricular, supraoptic and accessory magnocellular nuclei are sensitive to stressors influencing body water and electrolyte homeostasis.

One of the most important nuclei in the hypothalamus is PVN. The neurons (parvocellular subdivisions) synthesize and release CRH (and ACTH corticosterone) and vasopressin, which is the beginning of the efferent pathway in the stress reaction.

The lateral hypothalamus is rich in interneurons and is the 'connecting station' between the medial hypothalamus, the limbic system and the autonomic nervous system. Almost all of the stress-conducting fibres enter the hypothalamus in this lateral area. The lateral hypothalamus is also important for food intake (formerly viewed as the hunger centre).

Structures of the limbic system: The strong interconnection between stress and emotional circuits has been proven multiple times[44,45], and both cortical and subcortical limbic structures are involved in the response to stress. The subcortical areas (amygdala, septum, habenula and related structures) receive the projection from the brainstem and connect to cortical (or subcortical) structures of the limbic system. The amygdala (central nucleus) contains various types of peptidergic neurons (CRH, somatostatin, neurotensin, enkephalin and galanin) and forms circuits (brainstem–amygdala–brainstem, and hypothalamus–amygdala–hypothalamus (PVN)). The cortical area (the limbic cortex) consists of the hippocampal formation (hippocampus, dentate gyrus and subiculum), and entorhinal, piriform, prelimbic, intralimbic and cingulate cortices[46].

The limbic system is responsible for many types of behavioural responses to stress. Thus, the limbic system is part of long circuits, as defined by Pacak and Palkovits[3] (brainstem and spinal viscera- and somatosensory neurons $\rightarrow$ limbic system $\rightarrow$ brainstem and spinal autonomic preganglionic neurons). Limbic projections to the hypothalamus may affect the neuroendocrine hypothalamopituitary system. The septum constitutes an interface between the hippocampus and the hypothalamus. Limbic cortical regions are sensitive to stress, especially if the stressor exceeds a noxious threshold[3]. These regions are neuronally connected with the hippocampus (directly or through entorhinal neurons) and are responsible for stress-related motivational and behavioural responses.

Other structures: Besides the specific neurotransmitter groups involved in the processing of stress responses, there are other circuits that are important in the reaction to stress.

(i) Danger pathways – 'Danger pathway' is a term for different neuronal circuits (brain and brainstem) that are activated by physical, chemical and immune stressors. These circuits comprise of mainly monoaminergic neurons described above. However, some findings support the role of histamine in the danger response[47].

(ii) Circumventricular organ neurons – The blood–brain barrier is not impermeable as a whole, but there are some areas allowing the passage of different molecules from and to the brain. These parts are called circumventricular organs, and the cells in the organs are passive and active participants in the signalling from the body to the brain. Cells of the lamina terminalis react to changes in water, electrolyte homeostasis and blood pressure. These neurons project to parvocellular neurons of the PVN in the hypothalamus, where angiotensin II receptors and other hypothalamic nuclei (ncl. preopticus anterolateralis and ncl. dorsomedialis) are activated.

(iii) *Neurons of nucleus interstitialis striae terminalis* – This nucleus consists of sub-regions that are differently involved in a stress reaction. The anteroventral part is able to activate the HPA axis, the anterolateral part of which consists of neurons projecting to the PVN (GABAergic), which indicates that this part inhibits HPA activation. The effects on the cardiovascular system (an increase or decrease in blood pressure dependent on wakefulness) are not uniform and, therefore, the role of this nucleus should be clarified in the future.

Efferent pathways of stress reaction

The central processing of stress signals results in the efferent signalling that comprises of neuronal and neurohumoral components. These components affect the organism in orchestration. The neuronal reactions are mediated via visceromotoric and somatomotoric nerves. The hypothalamus, limbic system and neocortex have modulatory effects on the responses to stress (tonus of autonomic nerves, thermoregulation, and ion and water homeostasis). The hypothalamus has a specific neuro-humoral efferent system (the HPA axis), which is the most important neuroendocrine system in the stress reaction[48].

The stress reaction comprises coordinate activation of many effector neuronal and humoral pathways. The most important are the sympatho-adrenal system and HPA axis (Figure 2). Both have central and peripheral parts, are anatomically and functionally interconnected and can react at different levels during stress. For example, HPA axis hormones affect the activity of the sympatho-adrenal system on the brain, hypophysis and the adrenal medulla level. The integrative part of these systems are neurons of the PVN, lateral hypothalamus and brainstem, which directly innervate sympathetic preganglionic neurons and thus regulate the activity of the sympatho-adrenal system[49]. The most important hypothalamic structures are the magnocellular neurons of the PVN that release vasopressin (an antidiuretic hormone) and the PVN parvocellular neurons that synthesize CRH. Thus, PVN can be considered as the main integrative nucleus in the stress reaction. PVN projects to the brainstem and spinal cord and thus regulates autonomic nervous system activity. Nerve endings from parvocellular neurons project to the eminentia mediana where CRH is liberated into blood circulation. PVN also receives signalling from other parts of the CNS (or periphery): (a) visceral and nociceptive signals, and signals from thermoreceptors (via tr. spinohypothalamicus, NTS and catecholaminergic neurons in the medulla oblongata; (b) humoral signals (directly passing the blood–brain barrier via circumventricular organs or nervus vagus – NTS – A1/C1 catecholaminergic neurons); (c) limbic inputs from the orbitomedial prefronatal cortex and amygdala are connected to ncl. interstitialis striae terminals and ncl. dorsomedialis hypothalami, and (d) intrahypothalamic projections (ncl. dorsomedialis, ncl. suprachiasmaticus, ncl. arcuatus and area periforniclais).

Central noradrenergic neurons (LC) are another part of the stress effector pathway that affect peripheral organs. The adrenal gland consists of two phylogenetically different parts: the medulla (ectodermal origin and it develops from neural tube cells and produces adrenalin and noradrenaline), and the cortex (mesodermal origin and produces corticoids, i.e. glucocorticoids and mineralocorticoids). In addition to the sympatho-adrenal system and HPA axis activation, the stress reaction as an efferent pathway also activates many systems that are important in coping with strain to the organism. Interconnections between the hypothalamus, thalamus, limbic system, reticular formation activation system and cortical structures are believed to play this role. In detail, cortical structures are responsible for modulation of awakeness, cognition and vigilance. The limbic system (amygdala and hippocampus) modulates emotional aspects of stress reactions. The thalamus can be considered as an integrative centre of sensory and sensitive information from the periphery and senses that integrate this signalling with parts of the limbic system, hypothalamus and associative cortex. The hypothalamus coordinates the endocrine and autonomic nervous system response. The reticular formation activation system modulates pain, autonomic nervous system activity and muscular tonus.

Changes in the CNS: The efferent stress systems, HPA and catecholaminergic systems have been reviewed above. The levels of hormones/neurotransmitters (mediators) related to these glands are significantly elevated during/after stress. This is true in the case of catecholamines (epinephrine and norepinephrine), corticotrophin releasing hormones (CRH), adrenocorticotropin (ACTH) and glucocorticoids (corticosterone). Some findings,

however, raise the question about the role of ACTH in the process of some stress responses[50]. In contrast, CRHs appear to be an indispensable component of the stress reaction[51].

On the other hand, evidence about different mediator systems activated during stress is increasing. This is especially true in the case of the CNS when the integration and orchestration of stress signalling is provided through delicate interconnections between different neurotransmitter/receptor systems (e.g. GABA, glutamate[52], CRF, norepinephrine[53], serotonin, dopamine, muscarinic cholinergic[54], vasopressin[55] and many others). Moreover, corticoids can act in the brain not only via glucocorticoid receptors, but also by targetting the mineralocorticoid receptors[56].

When concentrated to muscarinic receptors (MR), as reviewed by Myslivecek and Kvetnansky[18], it is possible to find many examples in which these receptors are activated during stress response. These may serve as paradigms which show that not only 'classical pathways' are activated, but so are alternative neurotransmitter systems that are involved in the stress reaction. For example, cold stress[57] decreased acetylcholine content, increased the release of acetylcholine and increased MR density in the hippocampus. Food restriction enhanced the facilitatory effects of the muscarinic agonist oxotremorine and also reduced the impairing effects of atropine on passive avoidance[58]. Pontine and hippocampal MR (M_2) were reduced after sleep deprivation[59]. Li and Ku[60] showed the importance of MR in the emotional pressor circuit. They demonstrated that the lateral septum-habenula (and habenula-posterior hypothalamus) and the locus coeruleus–rostral ventrolateral medulla pressor system are components of the amygdaloid nucleus–emotional pressor circuit and that the cholinergic system is important in each nucleus of this circuit. Also, immobilization stress affects MR in several brain areas, such as the caudate–putamen, cortical layers and CA1 field of the hippocampus, among others[61].

It is necessary to note that MR is not the only neurotransmitter receptor that is affected by a stress reaction. It is evident that other neurotransmitter/receptor/effector pathways play roles in stress response (serotonine, dopamine, GABA, glutamate, CRH, vasopressin). Therefore, it is necessary to understand the central processing of stress and efferent pathways not only as the issue of catecholaminergic neurons, non-catecholaminergic neurons, hypothalamic nuclei and the activated HPA axis, but also as a response in which multiple molecular mechanisms are involved.

Changes in the peripheral tissue: The picture of changes in peripheral tissue is complicated, as interconnections between neurotransmitter systems in peripheral tissue exist. In the peripheral tissue, the function is regulated by multiple mechanisms and, therefore, stress can affect multiple systems. For example, in the colon, neurokinin NK1 receptors are affected by stress[62]. A decrease in MR in the small intestine after repeated cold stress was observed[63]. The cold exposure (between 4 and 7 days) decreased MR density and increased the nicotinic receptor density in adrenal tissue homogenates[64]. Immobilization stress was able to decrease lung adrenoceptors and muscarinic receptors, and these changes were gender-specific[65]. This fact could imply that more mechanisms can participate in the stress reaction. There are at least two possibilities for how to explain the involvement of other neurotransmitter/receptor systems: (i) The roles of the other systems are independent, and the systems are activated simultaneously with the above-mentioned stress response elements (i.e. 'classical pathways'). (ii) There is a mutual interconnection between the parts (mediators) of the HPA axis, or catecholamines with other system(s), i.e. ACTH–other system, glucocorticoid hormones–other system and catecholamines–other system interactions are responsible for the participation of other systems in stress response.

The effects of stress reaction on vital and CNS functions: As stressors elicit the activation of stress response elements that are tightly connected with elevated catecholamines, it is no surprise that many vital functions can be affected by stress. In that context, stress influences the cardiovascular system[2]. The increased levels of catecholamines are considered as an important factor in the development, progress and treatment of heart failure[66–68]. Stress is also one of the factors contributing to the development of asthma[69]. But, importantly, gender differences may also play a role in asthma development[70–72], which also coincides with receptor changes during stress[65]. Stress plays a role in anxiety disorders, depressive illness, hostile and aggressive states, substance abuse and post-traumatic stress disorder[10]. Moreover, stress is also able to affect biological clocks (i.e. circadian rhythmicity), which it is sometimes overlooked[73]. Finally, the concept of allostasis was elaborated further to create the concept of social allostasis[74], which gives the concept of allostasis new dimensions and shifts our knowledge to other levels.

Concluding remarks

Stress is a complex reaction of an organism to strain. This reaction is stimulus-specific, i.e. different stressors activate different pathways that are specifically processed in the CNS. Although stress is able to elicit disturbing changes in the organism, it is not only a devastating event but can also have, in some circumstances, positive effects on the organism (see eustress in Seley's definition[5]). In addition, the negative connotation of stress should be corrected, as it (if there is not an allostatic overload) can help an organism survive. Although catecholamines and HPA pathways can be considered the most important

stress pathways, multiple findings show that other neurotransmitter/receptor/effector systems are also activated (either simultaneously or secondarily to the classical pathway).

In summary, stress is a complex reaction with stressor-specific pathways. Stress can also be seen as a reflex reaction/behaviour in which the afferent pathways are represented by the activation of receptors at the centre by the stressors, which is a complicated network (relationship) of specific areas of the CNS; the effectors (efferent pathways) are represented by systems activated in order to optimize the organism reactions. Stress helps organisms survive and, therefore, it cannot and should not be avoided.

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ACKNOWLEDGEMENTS. This work was supported by The Ministry of Education, Youth and Sports – Institutional Support for Long-term Development of Research Organizations – Charles University, 1st Faculty of Medicine, PRVOUK P25/LF1.

Received 23 September 2013; revised accepted 9 June 2015