Don‘t threat me, it makes me cold! Evidences for threat/stress-induced hypothermia

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The model presented in this paper offers a more detailed picture of the stress/threat response cascade by adding 3 new sequences to the known one: stress/threat-induced hypothermia, stress/threat-induced GABAergic hypofunction, and altered inhibitory/excitatory neurotransmission ratio. The statement that threat causes hypothermia is contrary to the accepted paradigm of stress-induced hyperthermia. The arguments that threat induces hypothermia rest on principles of homeostasis, thermoregulation, psychopharmacology and equality with the cold shock response. According to this model, the *initial appraisal* of a stimulus as a threat causes *hypothermia which will be followed by primary GABAergic hypofunction,* as a *common trigger, which governs simultaneous alteration of the firing rate and functioning level of separate neural pathways.* This alteration manifests in emergence of the components of the response to threat: signs of upper motor neuron, visceral, and psychological symptoms as the end of the threat/stress response cascade.

Introduction

The basic ideology of the influence of the stimulus over the motor, visceral, and emotional functioning of the individual who came in contact with it dates back to the Aristotle, Plato, the Stoics, Spinoza. W. James (1884) postulated the first widely influential theory of interaction between an individual and a threat. According to him, it is the afferent proprioceptive signals from the bodily changes, especially fluctuation in visceral responses, mediated by signaling from these motor and sensory centers that account for the emotional experience.

This was directly challenged by W. Cannon who noticed that similar visceral changes and autonomic activation seem to occur across a spectrum of both emotional and non-emotional states, and are thus “too uniform to offer a satisfactory means of distinguishing emotions […] very different in subjective quality” (Cannon, W. B., 1927). According to Cannon and P.Bard both the experience of the emotion and the bodily response occur at the same time, independently of each other. Cannon considered that the spectrum of an individual’s responses to exterior or interior stimulus, which he named as a “fight or flight response”, has to be triggered in an effort a boost of energy to be created through: a) general discharge of the sympathetic nervous system (SNS), and b) activation of the adrenal gland through HPA Axis, priming them for fighting or fleeing (Cannon, W. B., 1915).

Selye accepted Cannon's "fight-flight response" which he saw as a part of the "alarm stage" and defined two more stages: Stage 2 - a stage of resistance, with enhanced pituitary gland secretion, high cortisol, atropine, and noradrenalin concentration, and Stage 3 - a stage of exhaustion, when real disorders appear: high blood pressure, allergies, psychosomatic disorders, etc., which he named *general adaptation syndrome- GAS* (Selye, H., 1976). According to him, the responses to the stimulus which has been appraised as a threat are *non-specific,* meaning that the spectrum of reactions will be always *equal* and *independent* of various agents that cause stress (Selye, H. 1976). Selye recognized that the same physiological processes which at the beginning of the response to a threat have been assumed as protective are practically an initiation of somatic disorders that, during the time, shorten the lifespan of the individual exposed to chronic stress. In other words, the experienced and repeated threat causes additional threats to the individual through appearance of somatic disorders. One circulus vitiosus starts. His theory has become accepted in almost all forms of human discourse about life and health, and psychologists and scientists use the stress as a unifying concept to understand the interaction of organic life with the environment.

In the 1960s, M. Arnold developed her cognitive theory, where she specified the appraisal of the situation as the first step in emotion. With it, she drew attention towards what happens right after the contact between the stimulus and to him specific receptor (Scherer, K. R., Shorr, A. & Johnstone, T. (Ed.), 2001). She stated that the initial appraisal starts the emotional sequence and arouses both the appropriate actions and the emotional experience itself, so that the physiological changes, […..], accompany, but do not initiate, the actions and experiences (Arnold, 1960). Like Cannon, she also supposed that *separate pathways* are responsible for both the appropriate actions and the emotional experience which occur at the *same time independently from each other*. She pointed out that within initial, intuitive appraisal, the emotions will be roughly distinguished between good or bad, which define the action of the person.

Close to Arnold´s terms of appraisal theory examination, Lazarus continued to research emotions through appraisal theory. According to him, the appraisal process is broken up into two different categories, primary appraisal and secondary appraisal. In a *primary appraisal,* the person evaluates two aspects of a situation: the motivational relevance and the motivational congruence (Lazarus, R. S. & Folkman, S., 1984). This state failed to hold up under scholarly and scientific critique, largely due to the fact that it fails to account for the often rapid or automatic nature of emotional responses (Marsella, S. & Gratch, J., 2003)

Appraisal as a sequence of responses to threat/stress found place in the theories that emerged later: the Two Factor Theory of Schachter and Singer (Schachter, S. & Singer, J., 1962), Smith and Kirby´s Two Process Model of Appraisal (Smith, C. A. & Kirby, L., 2000), Scherer's Multi-level Sequential Check Model (Scherer, K. R., 2001) or Roseman's Theory of Appraisal (Roseman, I. J., 1996).

Threat and body temperature

There are indications that stress influences the body temperature (Tb) in humans. Stress-induced hyperthermia (SIH) has been assumed to be an integral part of an individual's response to situations perceived as threatening or distressing by that individual (Olivier, B. et al., 2003; Briese, E., 1995) and has been used to detect putative anxiolytic-like properties of psychoactive drugs (Van der Heyden, J. A. M., 1997; Spooren, W. P. J. M. et al., 2002). There is quite some discussion in literature about the mechanisms and mediators of SIH (Oka, T. et al., 2001), as well as whether the rise in body temperature (Tb) upon encountering a stressor is a real fever or a hyperthermia. There are assumptions that fever is reflecting a centrally regulated rise in Tb set point that can be enhanced for an extended period of time (hours to days), or that thermoregulation might demand differential control under these conditions (Oka, T. et al., 2001). Olivier et al. (2003) and Vinkers et al. (2009a) referred to it as "merely a hyperthermia".

Looking at the motor (S. 6.1, Fig.1), visceral (S. 6.2), and psychological (S. 6.3) responses observed immediately after appraised threat: increased muscle tone, peripheral vasoconstriction, piloerection, accompanied or not by a fear, it strikes that all of these symptoms are identical to those observed in a cold shock. The cold shock includes the initial responses evoked by the immersion of an unprotected body in cold water, as an impact of a large and fast fall in skin temperature resulted from the transfer of the body heat to the cold surrounding. It includes an "inspiratory gasp", hyperventilation, hypocapnia, tachycardia, peripheral vasoconstriction, and hypertension. The responses are very quick - they reach a peak within 30 s of immersion, and adapt over the first 3 minutes of immersion in most individuals, but the inspiratory gasp occurs almost immediately upon immersion (Datta, A. & Tipton, M., 2006).

The function of the changed functional level of the upper motor neuron and sympathetic nervous system in the cold shock is a positive heat balance to be reached in a very short time, through a) increased muscle tone - a big amount of thermal energy (heat) to be released, and b) peripheral vasoconstriction and piloerection - the heat loss from the body to the cold surrounding to be reduced. In case a positive heat balance could be reached, it will enable Tb to start to increase until Tb set-point is regained, as one of the most important variables for stable milieu intérieur. Considering the equality of symptoms manifested in a threatening situation and a cold shock, it seems that the appraisal of a stimulus as a threat (S. 2, Fig.1) must be causing a drop of Tb (S. 3, Fig.1), the upper motor neuron (UMN) and the SNS, as thermoregulatory mechanisms to cold, to increase their tone.

Why does the body, in threatening situations, response with mechanisms underlying the thermoregulation in cold environment? Homeostasis means that the brain coordinates the body systems with the aim of maintaining a set of goal values for key internal variables, adjusting the internal environment to maintain stable equilibrium in response to changes in external and/or internal conditions. According to the principle of the homeostasis, the changes in the neuro-physiological functioning level will be undertaken just *in the case a real change* of the prior value of one or more physiological variables happens. It means that the increase of muscle (S. 6.1, Fig.1) and sympathetic tone (S. 6.2, Fig.1), as the quickest thermoregulatory mechanisms to cold, will occur only if the Tb drops, which indicates that the appraisal of a stimulus as a threat somehow causes the Tb drop: real hypothermia that triggers the thermoregulatory mechanisms to cold with the goal the Tb set-point to be regained. Release of an amount of heat without a prior change of Tb is not possible if the principles of the homeostasis still hold. Homeothermic animals, including humans, rigidly regulate their core body temperature through a variety of involuntary thermoregulatory responses, such as shivering (muscles), and non-shivering: thermogenesis, cutaneous vasomotor responses, piloerection, sweating (Nakamura K., 2011).

Regulation of the body temperature is a complex and vital process governed by the central nervous system. The maintenance of the temperature set-point is one of the most important variables of inner milieu. The hypothalamic preoptic area (POA) is the main thermoregulatory integrating center that contains a heat-loss center with warm-sensitive neurons and a heat-promoting center with cold-sensitive neurons which are affected by local and peripheral temperatures (Jha, S. K. et al., 2001; Boulant, J. A., 2000). Hypothalamus plays a key role in

regulating autonomic function, usually as part of more generalized, quite stereotyped, behavioural responses triggered by internal challenges (e.g., a change in Tb) or external threats (Dampney, R. A. L., 2011). In adults, hypothalamus GABA is the primary inhibitory transmitter, found in 50% of the presynaptic boutons (Decavel, C. & Van den Pol, A. N., 1990), which regulates the intensity of the stress response (Bondarenko, E. et al, 2015).
In normal conditions, GABA acts through GABA-A receptor in modulating the spontaneous activity of thermosensitive neurons in the POA and modulates the Tb (Jha, S. K. et al, 2001; Boulant, J. A., 2000; Nikolov, R. P. & Yakimova, K. S., 2008).

After exposure to cold, the activity of the warm-sensitive neurons of the dorsomedial nucleus of the hypothalamus (DMH) decreases, and, depending on the degree of the drop of the Tb, subsequently leads to heat conservation (through vasoconstriction) and/or heat production (shivering) via neurons that project directly to the rostral raphe pallidus (RPa) (DiMicco, J. A. & Zaretsky, D. V., 2007). If we argue that the motor and visceral component of the stress response are actually a thermoregulatory response to the drop of Tb: hypothermia (S. 3), how can the so well documented SIH be explained?

Looking more carefully at the results of some studies which report SIH, such as drop in tail and paws temperature in rats (Vianna, D. M. & Carrive, P., 2005), or decreased temperature in distal skin location such as a fingertip and finger base, (Vinkers, C. H. et al., 2013) we could also recognize a participation of thermoregulatory responses to cold in them. It is known from the physiology that the changes of the blood flow of the fingers are especially effective for the regulation of the heat loss because their surface area per unit mass is high, and that "the cutaneous blood flow, especially in uncovered skin areas, such as the hands, feet, lips, ears and nose is reduced almost entirely by the action of SNS in responses to changes in internal body or environmental temperature" (Blatteis, C. M. (Ed.), 1998). On the other hand, the reality is that even if Homo erectus left central Africa and populated Western Europe around 1.2 million years ago (Hopkin, M., 2008) the thermoregulatory mechanisms to cold have not still adjusted perfectly to the hypothermia.

The imperfection of the thermoregulatory response to hypothermia manifests itself in one excessive, over-shooting muscle contraction which, in combination with a strong peripheral vasoconstriction, could result in excessive positive heat balance. Due to this hyper production of heat, the temperature will start to increase, reach the set-point and continue to rise, causing

hyperthermia: SIH which corresponds to the results of Bouwknecht, Olivier, and Paylor (2007) and Bittencourt, Melleu, and Marino-Neto (2015) who found a short time rise of the temperature followed by a long-lasting and substantial decrease in Tb.

One other explanation on why after exposition to a stressor hyperthermia but not hypothermia has been measured lies in the measurement methodology. Generally, the timing is especially critical element in the methodology. Having in the mind that the manifestation of the motor, visceral, and emotional component of the response to the appraised threat is autonomic, immediate, and ultrafast - which means that muscle contraction and peripheral vasoconstriction happen within the first milliseconds, measurement of the body temperature 1 minute after the exposition to shock/stress (Olivier et al., 2003) is made too late, because the period of one minute is enough time the stress-induced hypothermia to be corrected by excess of positive heat balance.

Threat and Inhibitory vs. Excitatory Neurotransmission

From the point of view of the neurotransmitters functioning level, components of acute response to threat: a) motor component in the form of involuntary increase of muscle tone as a sign of upper motor neuron, b) visceral component: peripheral vasoconstriction, piloerection as a sign of increased sympathetic tone (Wible, J. H. Jr. et al., 1988), and c) psychological component: fear (Davis, M. & Myers, K. M., 2002; Holmes, A. & Chen, A., 2015) have the same genesis: the GABAergic hypofunction (S:4). This assumption that GABAergic hypofunction is the origin of all the components of the threat/stress response finds support in the studies of Vianna et al. (2008), Olivier et al. (2003), and Vinkers et al. (2009b), which showed that administration of benzodiazepines (BDZ) before exposition to stressor diminished the SIH. The explanation is that due to BDZ enhanced GABAergic inhibition the muscles contraction will be weaker, i.e. less amount of heat will be released. At the same time, the sympathetic arousal will be lower, the peripheral vasoconstriction will be less pronounced, and the loss of heat will be higher.

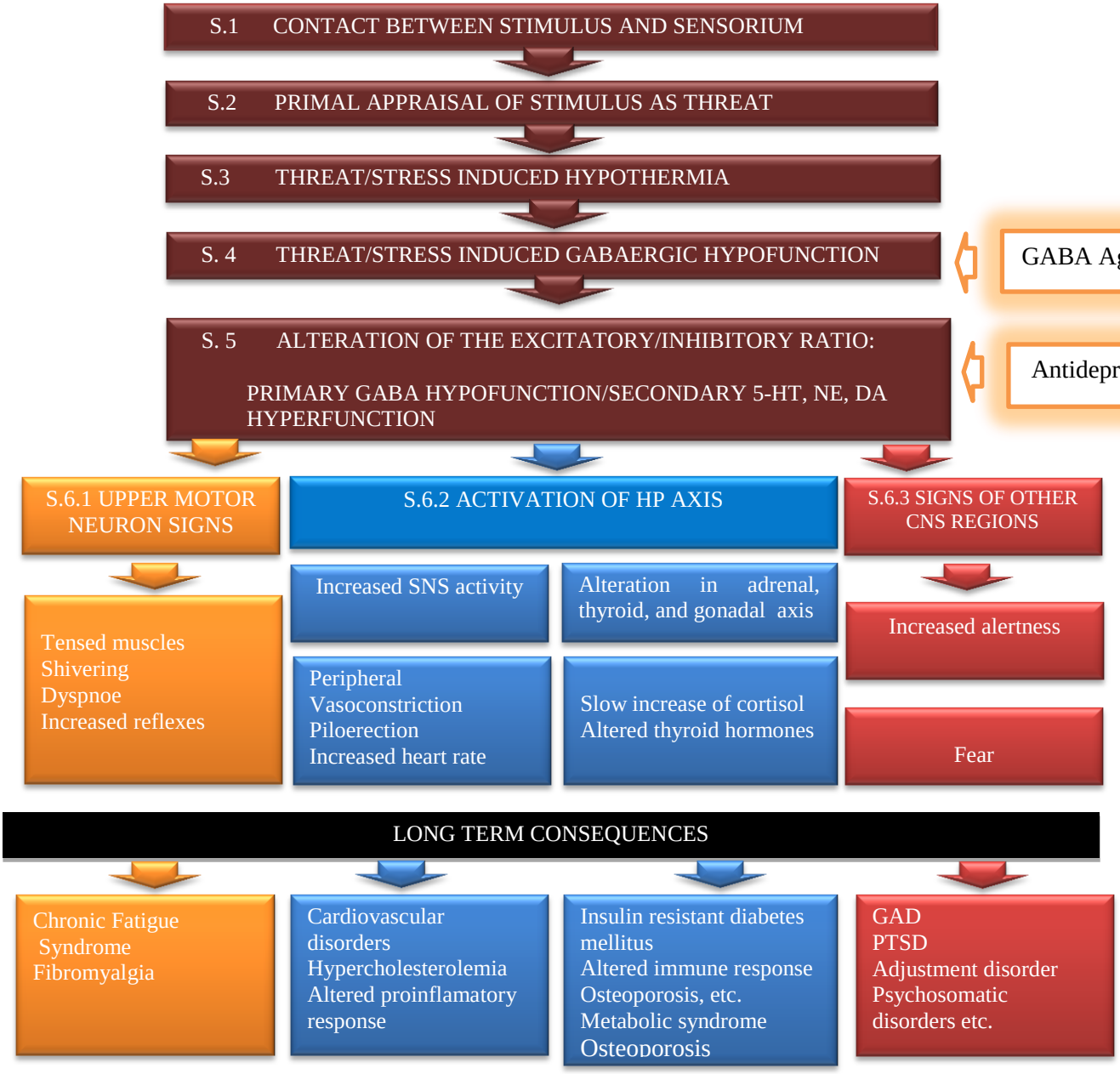

Fig. 1 Model of stress induced hypothermia and places of action of GABA Agonists and Antidepressants (A.Dimova)

GABA-Gamma-Aminobutyric acid, NA-noradrenaline, DA-dopamine, 5-HT-serotonin, SNS-sympathetic nervous system, HP Axis- hypothalamic–pituitary axis

On which step the drop of the Tb reduces GABAergic inhibition is unclear. Generally, it has been known that "alterations in temperature affect the rates of diffusion through ion channels, the rates of conformational changes that lead to their activation and inactivation, and the rates of the biochemical reactions with which ion channels are modulated and transported into and out of membranes" (Buzatu, S., 2009).

The Tb drop is one ongoing process which will be followed by a progressive diminishing of the GABAergic neurotransmission. (S.4). With a reduction of the inhibitory GABAergic

neurotransmission, the neurotransmitter systems which are under its control will be gradually unchained from this control, and start to behave in a hyperactive manner. As much the inhibitory GABAergic neurotransmission reduces, that much the hyperactivity of excitatory neurotransmitter systems, like serotonin (5-HT), noradrenalin (NE), dopamine (DA), etc., assumes more power (Fig. 2). Practically, it is a matter of secondary threat-induced excitatory hyperfunction (S.5; Fig.2).

The findings of increased activity of different brain structures within fear conditions, like in subcortex and cortex (Damasio, A. R. et al., 2000), somatosensory cortex, cerebellum (Koutsikou, S. et al., 2014), or amygdala (Costafreda, S. G. et al., 2008), could be explained through this secondary hyperactivity.

Fear and the inhibitory/excitatory neurotransmission ratio

Cannon was the first who recognized that the fear is a possible, but not obligatory psychological component of the response to threat. Usually, when we talk about the psychological component of the response to threat, we think of fear, which, from the aspect of the neurotransmitter functioning level, is an expression of the GABAergic hypofunction (Holmes, A. & Chen, A., 2015).

But, the fear is not the immediate response to threat. The state of increased alertness (IA) (Fig.2) as a psychological state emerges before fear. The reason this particular state of alertness, as a component of the response to threat, to be missed is its short duration. During IA, the individual exposed to threat appraises the stimulus more exactly, which increases the chances of more reasonable, efficient steps in confronting the threat. If we consider the drop of the Tb as a dynamic process, with the ongoing drop of the Tb the GABAergic inhibitory neurotransmission will diminish directly proportional to decrease of the Tb, followed by a consequent enhancement of the excitatory neurotransmission. The GABAergic/excitatory neurotransmission ratio will dynamically follow this drop of Tb in a sense of a dominance of excitatory neurotransmission. At one point, the inhibitory/excitatory neurotransmission ratio which responses to the sequence of IA will be obtained.

The pharmacological experience with stimulants indicates that the IA complies with a particular GABAergic/excitatory neurotransmission ratio. Ritalin and caffeine, both

stimulants, increase the alertness through increase of the activity of DA, NA (Ferreiro, C. & Triggle, D. J., 2004), or 5-HT (Dews. P. B., 1984). Through their action over these neurotransmitter systems, the inhibitory/excitatory neurotransmission ratio alters into dominance of excitatory neurotransmissions.

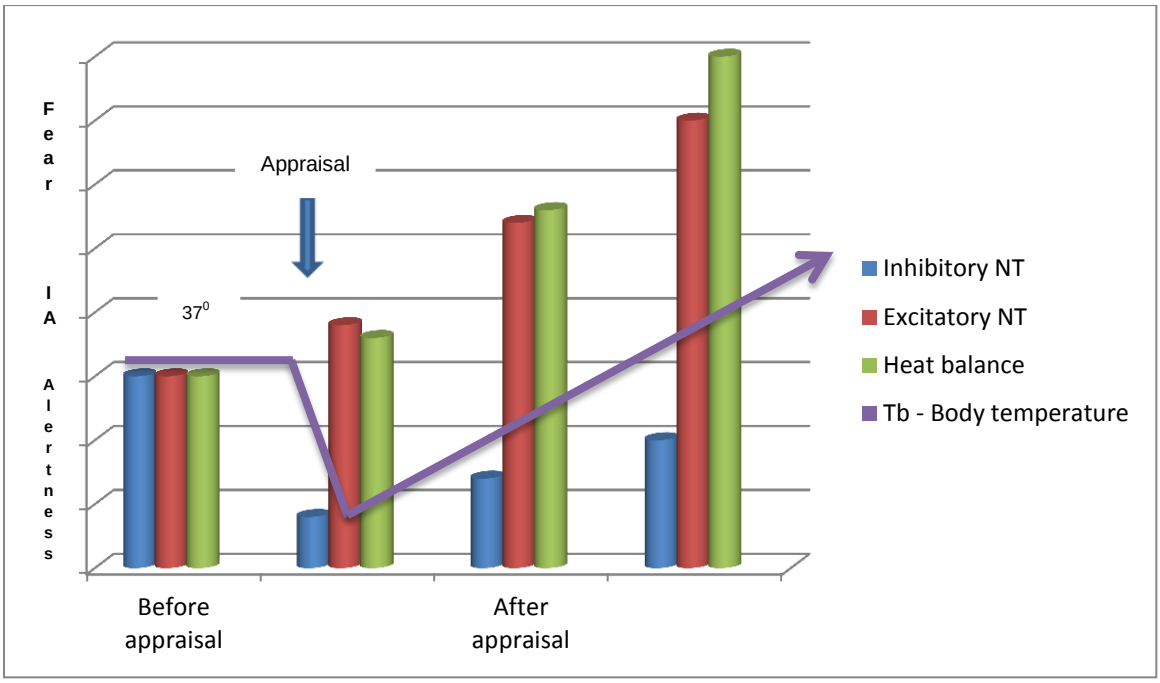

Fig.2 Hypothetic model of the alteration of inhibitory/excitatory ratio in the context of the change of the Tb after appraised threat and shift from state of alertness to increased alertness (IA) and fear and threat induced hyperthermia as possible consequence

The inhibitory/excitatory neurotransmission ratio, which responses to the state of increased alertness, should not be regarded as one definite value, but as a part of a continuum which with a further domination of the excitatory neurotransmission passes into fear. The meaning of the term IA in this paper corresponds to that state of alertness which enables "reasoning as a slower, more deliberate, and thorough process that involves logical, critical thinking about the stimulus and/or situation" (Marsella, S. & Gratch, J., 2003), and enables proper actions towards the appraised danger which could then really increase the survival chances of the individual exposed to threat.

The question is how long this particular inhibitory/excitatory neurotransmission ratio which enables more detailed perception of the stimulus and reasoning will endure. Duration of IA will be shorter as the drop of Tb is faster.

Conclusion

The model presented in this paper aroused from the known stress and appraisal theories, and rests upon the principles of homeostasis, thermoregulation, neurotransmission, psychopharmacology, and knowledge about psychiatric disorders. New sequences: 1. threat-induced hypothermia, 2. GABAergic hypofunction, and 3. altered inhibitory/excitatory neurotransmission ratio are added to the known threat/stress response sequences order. With the contact between the stimulus and the receptor (S. 1, Fig.1) the cascade of the threat/stress response starts. If the membrane potential reaches the value of action potential, this will give a starting shot the sequences of threat response to start to run. From that moment on, their flow is unstoppable, autonomous. With the next step: initial appraisal (S. 2), the dangerousness of the stimulus will be appraised, which defines the intensity of the threat response components: motor, visceral, and psychological. The initial appraisal is individual, which makes the response to a same stressor to be individual. In the case the stimulus is appraised as a threat, the Tb drops (S.3), the GABAergic inhibitory neurotransmission will be abolished (S.4) respectively to that Tb drop. The inhibitory/excitatory neurotransmission ratio in different brain regions (S.5) shifts toward a secondary excitatory hyperfunction. The alteration of the inhibitory/excitatory neurotransmission ratio leads to *simultaneous alteration of the firing rate in separate neural pathways* which manifests in emergence of the components of the response to threat (S. 6): signs of upper motor neuron (S. 6.1), visceral (S. 6.2), and psychological/psychiatric symptoms (S. 6.3) as the end of the threat/stress response cascade.

The *equality of the threat response components and the thermoregulatory mechanisms to cold* indicates that their function has to be regaining of the Tb set-point, not creating a boost of energy which prepares the body for a fight or flight.

Two crucial points of this model are: 1. the threat-induced hypothermia which is contrary to the widely accepted paradigm of SIH and 2. the threat-induced GABAergic hypofunction, as a common trigger of motor, visceral, and psychological components. The SIH has been understood as a side effect of the still unperfected adjustment of the thermoregulatory mechanisms to cold.

Primary vs. secondary, hypofunction vs. hyperfunction. From pharmacological point of view, the distinction between these conditions is very important. The rebalance of the GABAergic hypofunction/excitatory hyperfunction ratio could be pharmacologically reached by two approaches: a) enhancement of the GABAergic neurotransmission through GABA agonists,

and b) blocking the excitatory hyperfunction. GABAergic agonists are the most efficient anxiolytics, although hazardous, because of high abuse and dependence risk which require high caution in their usage.

Because of this risk, the usual way to treat the anxiety and depressive disorders is achieving a rebalance of the inhibitory/excitatory neurotransmission ratio with antidepressant drugs (AD). According to general assumption, the AD act over dysfunction of the 5-HT, NA, DA neurotransmitter systems, which means that in that way GABAergic hypofunction/excitatory hyperfunction ratio (Fig.1) will be rebalanced.

But there is preclinical evidence which suggests that the currently used AD which are designed to augment monoaminergic transmission may ultimately act to counteract GABAergic deficits (Luscher, B. et al, 2011), which supports the state of this paper.

Future perspectives

Based on the evidences presented in this paper the future research should be focused on measuring the Tb alterations, which means designing measuring instruments that are able to register immediate alteration of Tb which happens within the first micro-, even nanoseconds, after the appraisal of the stimulus as a threat occurs.

More studies which systematically investigate the effects of the stimuli appraised as a threat over the motor and visceral component observed in the context of thermoregulation and principles of homeostasis are necessary.

Having in mind that threat-induced GABAergic hypofunction triggers simultaneous alteration of many separate neural pathways, the first choice of drug treatment of the components of threat/stress response has to be rebalancing the primary induced GABAergic hypofunction by the next generation of GABAergic agonists that carry no abuse or dependence risk.

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