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Importance of TRP channels in pain: implications for stress

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1. ABSTRACT

Though stress is an integrated part of the modern life, defining stress in biological systems is difficult. Anxiety, medication, metabolic disorder, neuro-endocrinological abnormalities, immunological responses, neuro-immune interaction and several other internal and external factors are important which induce stress and pain in higher organisms. Stress and pain are often synonymous and overlapping to a large extent, but these two responses are different at the behavioral, cellular and molecular levels. Importance of Transient Receptor Potential (TRP) group of non-selective cation channels in the development and regulation of different forms of pain is well established. However, recent studies confirmed that TRPs can regulate neuroplastic changes through neuro-endocrine signaling, neuro-immune interactions and psychological state variables suggesting that abnormalities in TRP-signaling can indeed affect the hypothalamic-pituitary-adrenal (HPA) axis and several other metabolic pathways and thus may generate stress at various levels. Therefore, TRPs are important factors that can link stress with pain. This review summarizes the role of TRPs, their effects and clinical implications in the context of different types of pain which can be relevant for stress too.

2. STRESS AND PAIN: OVERLAPPING YET DIFFERENT GAME?

Due to changes in the modern life style and other associated factors, increased level of stress and pain has become a prominent clinical, social and economic problem (1). An increasing number of individuals worldwide suffer from chronic stress and pain. Both life quality and duration are adversely affected in these conditions. It has been predicted that chronic stress and pain-related problems are going to be the next biggest epidemic outbreak which makes the need to understand stress and pain at the molecular and cellular level. Understanding the relation between pain and stress at the behavioral context is a high priority and developing effective methods to nullify these responses are clinically important.

Apparently stress and pain seems to be synonymous and often overlap in many situations, mostly at the gross behavioral level. Stress can be defined as the nonspecific response of the body to any demand made upon it (2). Commonly, stress is referred to as any adverse condition observed at the cellular, organelle and/or individual behavioral level and is often associated with negative situations and settings (Box 1). Every individual

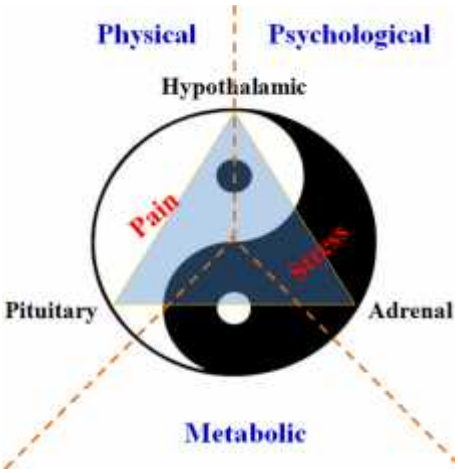

Figure 1. "Mind-body"- and HPA-axis are involved in feedback amplification of stress and pain. In altered conditions, physical, psychological and metabolic stimuli initiates individual perception of chronic stress and pain. If prolonged, stress and pain influence each other and forms a noxious cycle of negative events. This cycle is linked to the HPA-axis and affects the individual adversely. In addition, the HPA-axis also affects the physical, psychological and metabolic status of the individual and thus modulates the vicious cycle of stress and pain.

can handle stress to an optimal level which has been referred to as "eustress". In contrast, the stress which becomes harmful is referred to as "distress". The International Association of Study of Pain (IASP) has defined "pain" as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (Box 1). Pain is a sensation in a part or parts of the body, but it is also always unpleasant and therefore triggers an emotional experience. Pain is partly contextual. For example, it has been shown that pain sensitivity may or may not differ within the context of a conditioned fear response (3).

There are several common factors that correlate well with the development of stress and pain. In most cases, the causes, the outcomes and the symptoms of these two conditions are similar. Indeed, an increasing number of studies indicate that stress and pain often share a common "cause-effect" vicious cycle of events (Figure 1). This is because prolonged stress can be considered as an upstream event for the development of a chronic painful condition. In reverse, chronic pain can also induce severe stress at the physical and psychological level (4). Interestingly, both stress and pain seem to have a shared evolutionary origin. Certainly, pain is advantageous as it warns the body of potential damages. Similarly, a stress-free life may also be detrimental as an individual may lose his/her ability to react to the different challenges in a stress-free life. At present our understanding of stress, pain and their crosstalk is rudimentary, but these two seems to be different at the molecular, cellular and behavioral level. Thus, it might be possible to mark the boundary between stress and pain. Indeed, studies indicate that mis-regulation of ion channels is a key factor behind the development of chronic pain and other pathophysiological conditions. Therefore pain has been recently considered as a channelopathy (5-11).

So far stress and pain has been analyzed in terms of several factors/stimuli with different properties. Most of these factors can be categorized as physical or chemical stimuli (either endogenous or exogenous component). In addition, psychological stimuli are also involved in modulation of stress and/or pain (discussed later). As several studies have already identified the different physical and chemical stimuli contributing to pain development, this review will not repeat such information in further details. In contrast, this review will highlight the different psychological, neurobiological and biochemical factors and involvement of TRP channels that are relevant in the context of stress and pain.

3. FACTORS THAT GENERATE STRESS AND PAIN

It is known that certain physical stimuli like noxious temperature (hot as well as cold) and mechanical pressure can cause pain. However, the molecular basis of how different physical stimuli induce pain remains poorly understood. Molecular characterization of temperature-induced pain effectively started with the cloning of Vanilloid Receptor sub-type 1 (VR1) (12). This is commonly known as capsaicin receptor and now named as Transient Receptor Potential Vanilloid sub-type 1, (TRPV1) which can conducts a Ca^{2+}-influx in response to noxious temperature like 42°C (12). Subsequently, several other Transient Receptor Potential (TRP) channels were cloned and many of these are activated by noxious stimuli (like high or low temperatures, mechanical pressure) (13). TRPs were previously considered to be molecular detectors for physical noxious stimuli and associated with the transmission of pain signals. Therefore, TRPs are involved in the execution of noxious temperature- and pressure-induced deleterious effects. All these results in general indicate that TRPs are involved in thermosensation and mechanosensation (14). However, later studies confirmed that animals lacking these channels (knockout studies) have normal sensation suggesting the existence of functional redundancy among these closely related ion channels (15-17). For example, TRPV1 knockout mice have no thermal selection when tested against temperature gradients. However, the same animals reveal enhanced mechanical responses. Similarly, TRPV3 and TRPV4 knockout animals reveal a similar thermal preference comparable to wild type animals (18). These contradictory results indicate that TRPs may have overlapping yet different functions and signaling events relevant in the context of physiological sensation and pain.

In contrast to physical stimuli, chemical stimuli-induced acute and chronic pain development is relatively well-studied. So far a large number of studies have been conducted to identify and characterize several compounds (as exogenous or endogenous stimuli) that can induce and modulate acute or chronic pain (19-21). The endogenous components include different steroids and their derivatives, lipid metabolites, inflammatory and immune secretary

compounds (like histamine, interleukins, prostaglandins, bradykinin and others), growth factors (like NGF, BDNF, EGF), neuropeptides/ neurotransmitters (like GABA, SP, NPY), different hormones, other metabolic products, low pH and many other biomolecules (Table 1). These arrays of nociceptive molecules are recognized by a set of molecular detectors present in the nociceptive neurons and thereby induce pain (20). In most cases, different transmembrane-receptors, ion channels (including TRP channels) and pro-nociceptive kinases are the first set of target molecules that are stimulated by these nociceptive stimuli. Availability of these stimuli, expression and activity of these molecular detectors, and changes in the neuronal contacts are the prime factors that regulate the pain transmission and the degree of pain perception (21-23). In last few years significant progress has also been made to unearth the signaling pathways and cellular changes leading to the development of hyperalgesia and allodynia (Box 1). However, the detailed molecular mechanisms and pathways remain unclear and these pathways seem to vary depending on species and the stimuli used (21, 24).

In spite of extensive studies conducted to characterize different factors, still only few have been currently identified that can be considered as key effectors/modulators of pain (21, 25). TRPs not only act as key molecules that integrate several pain producing signaling events but also play a much bigger role as molecular regulators (26). Apart from their role in ionic conductance, these channels interact with several proteins and form dynamic signaling complexes at the membrane alternatively known as the signalplex (27). Further studies are needed to understand how different factors and stimuli can alter the organization, regulation and function of these complexes. A detailed biochemical and cellular understanding of these signalplexes has clinical and pharmacological interest too.

So far a magnitude of work has also been done to characterize stress-inducing physical and chemical factors (termed as stressors) and their effects. In contrast to different forms of pain, understanding the physical and biochemical basis of stress at the molecular level is just at its beginning and remains largely undefined. Though, the number of stressors is large, our understandings about the stressors, their mode of action and effects remain largely fragmented. Often the effects of different stressors differ largely in quality, quantity and from subject to subject. For example, changes in the day-light cycle perceived by individual can also be stressful for some while others may remain unaffected (27). So far very few endogenous bio-molecules have been identified in higher animals that can be considered as stress markers. The correlation of these markers with the actual development of stress also remains disputed. Thus, the outcome of all these studies can largely be categorized in parts: the effect of stressors at the level of metabolism and development of stressor-mediated abnormalities at the level of cell, tissue and/or behavior.

Interestingly, altered levels of a few bio-molecules (such as higher level of steroid hormones) correlate well with the development of stressed conditions. However, the reasons behind this altered level of steroids are not clear (28). It has been demonstrated that school boys who are occasionally bullied have higher levels of cortisol (Box 1) than their peers who are not bullied (29). In contrast, bullied girls seem to have cortisol at low levels (29). Similarly, elevated corticosterone in the amygdala increases anxiety-like behavior and pain sensitivity (30). Similarly, higher level of blood cholesterol positively correlates with the conditions characterized by hypertension, stress and depression (31-32). It has been demonstrated that depressed female primates have higher total plasma cholesterol (TPC) and lower level of high density lipoprotein cholesterol (HDLC) than non-depressed female primates (31). A contribution by the immune system in stress-response has also been demonstrated (33-34). However, it is difficult to make general conclusions based on these studies for several reasons. First, the molecular mechanisms behind the individual to individual differences are not clear. Second, the variability observed in these studies is generally large and often differs from species to species and population to population.

4. PHYSICAL, BIOCHEMICAL AND CELLULAR BASIS OF PSYCHOLOGICAL STRESS AND PAIN

Recent studies have confirmed that psychological state contributes robustly to the manifestation of pain and thus is referred to as psychogenic pain (35). Psychogenic pain has some common symptoms like headache, back pain, or stomach pain. Previously, this type of pain was considered an emotional phenomenon which is exclusively independent of stimulation or damage of the peripheral nervous system. However, later studies indicate that psychogenic pain is more complex in nature. Functional magnetic resonance imaging (fMRI) confirmed that sadness enhances the experience of pain via neural activation in the anterior cingulate cortex and amygdala (36). In a similar context, “Phantom pain” and “emotional pain” have a large degree of psychological association and these forms of pain can affect physiology too. “Phantom limb pain”, is a kind of neuropathic pain which is common in almost 85% of the amputees who report this type of pain in their amputated limb after surgery (37). Emotional pain is also another form of pain where psychological contribution is significant (38). High blood pressure, pain in the chest and heart, an abnormally elevated mood, inflated self esteem, acute insomnia, obsessive-compulsive disorder, anorexia, depression, loss of concentration, and tearfulness, are some of the commonly considered symptoms of stressful situations which are often brought by a romantic break up or by a "crush".

In contrast to pain, understanding the psychological contribution in stress is even more difficult as it affects the “mind-body” correlation by several complex mechanisms. Although a correlation (either positive or negative) exists between “mind-body interaction” and the development of stress and/or pain, how psychological states actually contribute to these conditions remains poorly understood. Why and how different individuals perceive stress with a different threshold level and gradually build or avoid stressed conditions also

Table1. Cross-talk between several stress-related factors and TRP channels

	Compound	TRP channel	Effect(s)
Neuropeptides	Neuropeptide-Y	TRPV1	Suppresses Ca^{+2}-influx via TRPV1
		TRPV1	Inhibits activity of capsaicin-sensitive nociceptors and decrease capsaicin-induced CGRP release
	Substance-P	TRPV1 & TRPV4	Contributes in vasodilation regulated by Substance-P during osmotic stress
		TRPV1	TRPV1 activation results in release of Substance-P from capsaicin -sensitive spinal cord afferent terminals
	CGRP	TRPV1 & TRPV4	Contributes in vasodilation regulated by CGRP during osmotic stress
Neurotransmitters	Dopamine	TRPV1	Activation of TRPV1 excites dopaminergic neurons and increases dopamine release
	NADA (Dopamine-derivative)	TRPV1	Activates TRPV1 and causes retraction of TRPV1 positive neuronal growth cones
	N-acyldopamines	TRPV1	Activate TRPV1 and causes Ca^{2+}-influx
	OLDA	TRPV1	Activate TRPV1, causes Ca^{2+}-influx and pain
	Oleic acid, NAE	TRPV1	Activate TRPV1, causes Ca^{2+}-influx
	Linoleic acid	TRPV1, TRPV3 & TRPM8	Increases open channel block (OCB) activity in which metal ion binds to receptor and decreases its ionic conductivity
	GABA	TRPC4	TRPC4 controls the GABA release from dendrites
	Glutamate	TRPV1	TRPV1 activation induces glutamate release from spinal cord synaptosomes
	Noradrenaline	TRPV1	TRPV1 activation stimulates release of noradrenaline
	Serotonin	TRPV4	Activates TRPV4 and results in Ca^{2+}-influx
Steroids and derivatives	Estrogen	TRPV1	Enhances the expression of TRPV1 channel in c-fibres
	Androgen	TRPV4	Reduces the expression of TRP4 in bovine aortic endothelial cells
		TRPV5	Activates TRPV5 and induces Ca^{2+}-influx
		TRPV1	TRPV1 activation induces expression of androgen receptor in prostate LNCaP cells
	Testosterone	TRPM8	Androgen regulates the expression of TRPM8
		TRPC3	Increases Ca^{2+}-influx in muscles cells
	Progesterone	TRPV4	Decreases the cationic current and Ca^{2+}-influx in human airways, mammary gland epithelial cells and vascular smooth muscle cells
	Insulin	TRPC5	Decreases activity of channels and Ca^{2+}-influx
		TRPV1	Present in islet beta cells and promotes insulin secretion and Ca^{2+}-influx
Protein hormones	Klotho	TRPC3	Interacts with GLUT4 and promotes glucose uptake
		TRPV5	Klotho, a β-glucuronidase hydrolyzes extracellular sugar residues on TRPV5 and increases Ca^{2+}-influx, prevents internalization and inactivation of the channels in Kidney cells
	Leptin	TRPC1 & TRPC4-7 TRPV1	Activates POMC neuron by generating action potential and causes Ca^{2+}-influx Activation of TRPV1 blocks Leptin-CCK regulation
	NGF	TRPV1	Increases expression of TRPV1, CB2, Leptin receptor and attenuate the ischemetic injury in brain
		TRPV4	Activates TRPV4 and sensitizes bladder for urine filling
Growth factors	BDNF	TRPV1	Sensitizes TRPV1 and causes Ca^{2+}-influx
	EGF	TRPC5	Effects rapid translocation, insertion of channels in the plasma membrane and causes Ca^{2+}-influx
	Transforming growth factor α (TGF-α)	TRPV3	Activates channels (in keretinocytes) and regulates proliferation, differentiation and also controls hair morphogenesis
	Transforming growth factor -β1 (TGF-β1)	TRPM7	Induces differentiation of fibroblasts cells and increases the expression of TRPM7
Immuno-secretory compounds	IL2	TRPM4	Prevents in T-lymphocytes and induces Ca^{+2}-influx and IL-2 production during T-cells activation
	IL4	TRPA1	Increases the production of inflammatory molecule during allergic condition in airway lungs
	IL5	TRPA1	Increases the production of inflammatory molecule during allergic condition in airway lungs
	IL6	TRPV1	Sensitizes TRPV1 via PKCδ pathway and produces pain
	IL13	TRPA1	Increases the production of inflammatory molecule during allergic condition in airway lungs
	Histamine	TRPV1/ TRPV4	Activates and excites sensory neurons by producing 12-HPETE, a downstream metabolite of PLA2 and LO (lipoxygenase)
	Bradykinin	TRPA1/ TRPV1	Activates TRPA1 which acts via GPCR and phospholipase-C pathways Causes excitation of vagal sensory airway pathways via nitration of TRPV1
	Prostaglandin	TRPV1, TRPV3 TRPA1	Sensitizes and activates TRPV1 Influences acute nociception and hyperalgesia by activating TRPV3 Directly activates TRPA1
	Macrophage Inflammatory Protein-2 (MIP-2)	TRPC6	Present in neutrophil granulocytes and promotes fast cell migration via rearrangement of actin filament
	IFN-γ	TRPV1	Increases intracellular Ca^{+2} due to production of inflammatory molecule in microglial cells
	NO	TRPV1 & TRPA1	Increases intracellular Ca^{+2} and expression of ion channels in DRG-neurons that helps in nociception
Other metabolites and byproducts	Reactive Oxygen	TRPA1	Increases intracellular Ca^{+2} and membrane current in lung sensory neuron
	Arachodonic acid	TRPV3 & TRPV4	Directly potentiates responses via TRPV3 expressing cells Activates TRPV4 and regulates cell swelling and metabolism of epoxyeicosatrienoic Acid,
	Acetaminophen	TRPV1	Induces analgesic effect by activating TRPV1 at the brain
	Epoxyeicosatrienoic acid (AA-derivative)	TRPC5 & TRPC6	Increases intracellular Ca^{+2} and also helps in translocation of channels to membrane in endothelial cells
	20-HETE (AA-derivative)	TRPC6	Activates TRPC6 channels
	12-(S)-HPETE (lipoxygenase product)	TRPV1	Activates TRPV1 and causes nociception
	15-(S)-HPETE (lipoxygenase product)	TRPV1	Activate TRPV1 and cause nociception
	5-(S)-HETE (lipoxygenase product)	TRPV1	Activates TRPV1 and causes nociception
	Leukotriene B4 (lipoxygenase product)	TRPV1	Activates TRPV1 and causes nociception
	LPS	TRPV2	Increases mobilization of intracellular Ca^{+2} via TRPV2 and IP3 receptor in macrophage cells

remains unclear. However, the psychological contribution in manifestation of stress and pain can further be explained on the basis of biochemical pathways. For example certain forms of pain can be reduced by using placebo and/or certain psychotropic drugs (23, 39-42). Interestingly, the placebo-induced analgesic effect is often gender specific suggesting that sex hormones might also be involved in this process (43). These placebo-induced analgesic effects can

be reversed by using Naloxone (a competitive antagonist of opioid receptors) suggesting that placebo, which is equivalent to a positive expectation, stimulates opioid pathways (44-48). In a similar fashion, Duloxetine (a balanced serotonin and noradrenaline reuptake inhibitor) is used for the treatment of major depressive disorders, urinary stress, incontinence and the management of neuropathic pain associated with diabetic peripheral neuropathy (42). Post-operative Phantom-pain can also be blocked by tricyclic antidepressants, namely by Milnacipran and Venlafaxine (a class of novel serotonin and noradrenaline reuptake inhibitors) (37, 41, 49-51). These indicate that psychology and neuro-chemical signaling events involving serotonin receptors play a role in case of phantom pain. Notably, memantine, milnacipran and ketamine (inhibitors of NMDA-receptor) effectively block phantom pain indicating that the involvement of NMDA-receptor in this process (41, 50, 52-53). Neuropathic and chronic pain inducing stimuli are known to increase the neuronal secretion of β-endorphin and down regulate transmission through the central μ-opioid and dopaminergic neurons (54). Often more than one pathways may interact functionally. For example, corticotropin-releasing factor and serotonin together contribute to the anxiety-related disorders (55).

A few studies have indicated that genetic factors contribute in the perception and amplification of stress and pain. Due to genetic variation, individual responses to local and changing environments varies and often initiates psychological and/or physical stress (56). For example, it is well-characterized that people exhibit changes in mood and behavior with changing seasons which are often characterized by anxiety, depression and stress. These changes are known as “seasonality problem” and termed as “seasonal affective disorder” (SAD) which is mostly hereditary. Indeed, gene variants of GABA (A) receptor, the μ-opioid receptor, the serotonin transporter, catechol O-methyltransferase (COMT), monoamine oxidase (MAOA), alpha (2)-adrenergic receptor, brain-derived neurotrophic factor and the anginotensin-converting enzymes are known to affect the HPA-axis in a different manner (57). The involvement of genetic factors in psychological stress and in schizophrenia (and several other psychological disorders) is best illustrated by the serotonin metabolism and signaling pathways (58). A few studies have indicated that promoter repeat length polymorphism of serotonin transporter (5-HTT, which is encoded by a single gene SLC6A4) correlates well with the onset of the mood and/or seasonal affective disorders (59-61). The promoter is characterized by insertion/deletion of 44-bp which generates either long or short allele of 5-HTT respectively. This shorter allele is a well-established risk factor for stress, anxiety, disorder in mood changes, food uptake and obesity in adolescents (54-64). In agreement with the involvement of serotonin in several disorders, enzymes involved in serotonin biosynthesize and factors involved in recognition and/or uptake of serotonin are also important genetic factors that contribute in psychological, physiological disorder (65). For example, mutations in the gene encoding for the tryptophan hydroxylase (TPH, the rate-limiting enzyme involved in serotonin biosynthesis) reveal psychological and physiological abnormalities including stress (65-66).

5. HPA-AXIS IN STRESS AND PAIN: IMPORTANCE OF TRP CHANNELS

Involvement of HPA-axis in stress was first demonstrated experimentally by H.F. Harlow. His experiments confirmed that physical separation of infant from mother induce strong stress to the infant as well as to the mother (67). Interestingly, prolong stress perceived in the early phase of development seems to have a long-lasting effect on learning and memory formation and seem to affect neural circuit like HPA-axis and limbic system (hippocampus, amygdala, prefrontal cortex etc.). At the behavioral level, attachment of infants with mother helps them to develop their learning circuit which is induced by maternal odor and nursing. Thus separation of infants from mother during early life shows several abnormalities in the later part (68-70). Often, the stress perceived by mother can be transmitted to the next generation too. For example, stress applied to rodents in the form of a physical exercise during pregnancy results in transient increases in postnatal hippocampal neurogenesis in the offspring after birth (71). Nevertheless, several studies indicate that psychology plays an important role in development or reduction of stress and pain. The exact nature, extent and pathways by which psychology modulates the mind-body interaction are different. Notably, the underlying mechanisms are not clear yet though the involvement of HPA-axis in stress and pain seems to be prominent (33, 72).

The altered behavior and function during stressful and painful conditions can partly be explained by changes in synaptic adaptations, neuronal structure, function, networking and alteration in the brain structures. Different forms of stress and pain can induce changes in the neuronal density (brain volume), number, subtype, connectivity, function, synaptic plasticity, neuro-immune interactions, neuro-endocrine secretion and regulation too. In that regard, changes in neuronal plasticity have been identified as a major link between stress and mood disorders (73). Stress seems to have a direct effect on the structure – function – regulation of the brain. For example, the amygdala plays a role in processing of anxiety and threat-related stimuli which are crucial in stress responses (74). A change in gray matter density within the bilateral amygdala has been associated with a stress response. In this context, reductions in stress correlate positively with decreases in right basolateral amygdala gray matter density (75). In a similar manner, acute psychosocial stress reduces cell survival during adult hippocampal neurogenesis (76). Similarly, stress-induced prefrontal cortical impairment has been linked with the development of mental illness. In addition, chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons and results in changes in the neuronal contacts as well as synaptic connectivity (77). In contrast, stress reduction correlates with structural changes in the amygdala (75). Reductions in stress also correlate positively with decreases in right basolateral amygdala gray matter density (75).

Similar to several stress-related disorders, changes in the brain structure and hypocortisolism seem to also occur during several painful conditions and thus have been considered as common characteristics of some functional pain syndromes (78-80). For example, patients with chronic pain perform impaired emotional decision-making tasks (79). By using Magnetic Resonance Imaging (MRI) technology, it was observed that patients with chronic back pain (CBP) had a reduction in the outer layer of the brain and have 5–11% less neocortical gray matter volume than control subjects (80). The magnitude of loss after normalization with the skull volume is equivalent to the loss observed following 10-20 years of normal aging. These studies strongly indicate that CBP is accompanied by brain atrophy and involves thalamocortical processes. It is noteworthy to mention that hippocampus plays a role in learning and spatial memory formation which is vulnerable in stressed conditions. Similarly, impairment in the prefrontal cortical has been linked with the development of mental illness induced by stress. A complementary effect on gray matter volume has also been observed by studying subjects who perform meditation regularly (81). It is well accepted that meditation has several positive effects and it improves psychological and physiological states (82). By using MRI it has been shown that long-term meditation correlates well with anatomical changes of the brain, especially in the right orbito-frontal cortex (as well as in the right thalamus and left inferior temporal gyrus. In addition, people performing regular meditation show significantly larger volumes of the right hippocampus. It is important to mention here that these regions are involved in emotional regulation and response control.

Noteworthy, TRPs can play a significant role in all these above-mentioned processes. Recent studies confirmed the physical and functional presence of different TRP channels (especially TRPVs and TRPCs) in specific regions of brain, namely in the thalamic and hypothalamic nuclei, locus coeruleus, periaqueductal gray, cerebellum, cortical and limbic structures which regulate the neuronal functions and networking in presence of stressor (83-86). In the same notion, involvement of TRP channels in schizophrenia and other neuropsychiatric problems have been suggested (87). Several endogenous and small molecules (such as endovanilloids, anandamide, estrogen, other steroids) have also been identified in the brain and other regions of central nervous system suggesting that these compounds can activate several TRPs either in a specific or non-specific manner (Table 1). For example, NADA, an endovanilloid can regulate neuronal structure, function and synaptic transmissions by activating TRPV1 (88). It has been reported that under stressed conditions, endocannabinoids within the paraventricular nucleus of the hypothalamus decreased excitatory inputs to HPA and cause release of corticotropin hormone into the portal blood at high levels as well as ACTH from anterior pituitary and corticosterone from adrenal gland. Similar results in general suggest that endogenous ligands of TRPs can regulate the behavioral responses and synaptic effects.

It is well established that TRPs regulate neuronal differentiation, networking and synaptic functions. Differential expression of TRP channels in DRG neurons helps in development of Isolectin-B4 (IB4) positive neuron (89). This in turn contributes to the maintenance of functional heterogeneity in sensory neurons involved in perception of touch (mechanoreceptors), temperature (thermoreceptors) and pain (nociceptor) (89). TRP channels are also involved in the regulation of neuronal functions which are related to cognition, pain perception and in neuropsychiatric disorders (90-91). For example, TRPV and TRPC channels are involved in neuronal survival, regulation of growth cone migration and neuronal networking (92-96). TRPC channels are involved in the migration of the growth cone and neuronal connection formation (93). Activation of TRPV1 also results in shortening of the IB4-positive nociceptive neurons and in the protection of hippocampal neurons against oxidative stress (97). In the same notion, TRPV1, TRPV4 and several other TRPC channels are localized in the synaptic sites (88, 98-99). At the synaptic sites, TRPs can modulate the synaptic organizations, regulations and transmissions and are involved with the release as well as uptake of several neurotransmitters and neuropeptides (Table 1). For example, recently we demonstrated that TRPV1 activation increases spine lengths (88). TRPV1 regulates metabotropic glutamate receptor and thereby regulate the function of dopaminergic neurons in rat (100). Activation of TRPV1 also induces release of substance-P and glutamate from synaptic sites. In the same notion, TRPC4 contributes to the control of GABA release from dendrites and can modulate the synaptic output. TRPV1 present in hippocampus neuron is known to increases long-term potentiation (LTP) and decrease long-term depression (LTD) (101). Genetic and behavioral experiments also confirmed that TRPV1 knockout animals (*trpv1* -/-) have reduced anxiety, conditioned fear, and hippocampal LTP (102). The increased LTP prevents the synaptic plasticity in hippocampus area and helps in learning in acute stress. However, the exact involvement of TRPV1 in LTP and LTD in CNS is still unclear. This is due to the fact that endogenous presence of TRPV1 in the microglia cells may add complexity under stressed conditions.

6. PHYSIOLOGICAL EFFECT OF CHRONIC STRESS AND PAIN

Stress is known to alter behavioral responses to certain stimuli which correlate with changes at the cellular and/or molecular level. As a result, neuronal connections, morphology as well as function are altered. These neuronal changes seem to be more prominent at the level of dendritic spines. While detailed characterizations of the biochemical and metabolic pathways that underlie these changes are still fragmentary, these changes have largely been analyzed at the level of gene expression and proteome. However, it is difficult to conclude if these changes in gene expression and the proteome are cause or effect of stress and/or painful conditions. Here we describe some of these changes in details.

6.1. Changes in the proteome and local protein synthesis

Few studies confirmed that the total proteome of tissues and cells, especially neurons are altered drastically

when subjects are exposed to chronic (both physical as well as psychological) stress and/or pain. Such studies have identified key proteins that show differential expression in normal and stressed/painful conditions (103-105). For example, 17 proteins were identified which are involved in anti-nociception (105). These proteins mostly represent factors involved in signal transduction, vesicular trafficking and neurotransmitter release, energy metabolism, and ion transport. Another study addressed the proteome changes of the synaptosome (isolated from spinal cord dorsal horn), especially after peripheral nerve injury (104). This study identified 27 proteins that are involved in transmission and modulation of noxious information, cellular metabolism, membrane receptor trafficking, oxidative stress, apoptosis, and degeneration. Another study indicated that nearly 200 proteins (representing cytoskeletal proteins, enzymes and proteins associated with oxidative stress) are up-regulated in hyper-excitable nerves (105). Notably, this work indicated that the differential expression was due to local protein synthesis which was altered in hyper-excitable nerves, a condition which correlates well with peripheral nerve injury-induced neuropathic pain.

Apart from direct regulation at the transcript level, post-transcriptional regulation seem to be another major mechanism by which chronic stress and pain can alter the proteome. Indeed, a proteomic study has revealed changes in the protein but not in the mRNA level of some proteins (unc-18 protein homolog 67K, CRMP-2 and CRMP-4) which are involved in the neurotransmitter release and/or axon elongation (105). The abundance of these proteins is regulated by post-translational regulation like proteolysis and/or phosphorylation. Similarly, another report confirmed the involvement of stress-granules, P-bodies and other transcript-related regulatory factors in stress and pain (106). For example, formation of stress-granules and P-bodies in DRG-neurons is regulated by many stress-related signaling events (106-107). In summary, these recent studies indicate that total protein synthesis at the cellular level and specific protein synthesis in sub-cellular regions like in dendritic spine have a profound role in stress and pain. Recently this hypothesis has gained credibility as it can explain many of the observed changes in the proteome in response to stress and pain.

Recent studies have demonstrated the involvement of microRNAs in the different forms of pain and stress (106-113). DRG-neurons of adult rats express three micro RNAs, namely miR-96, miR-182, and miR-183 which are involved in the regulation of mechanical hypersensitivity (106). Interestingly, miR-96, miR-182, and miR-183 are down-regulated in case of spinal nerve ligation, an experimental condition which correlates strongly with the development of neuropathic pain (106). MicroRNA-mediated regulation of dopaminergic neuron differentiation, expression of nociceptor-associated mRNA transcripts like Nav1.8, P2xr3, and Runx-1 and μ-opioid receptor has been linked with the regulation of pain (107-110). Regulation of TRPs by micro-RNA has also been reported recently. It has been shown that in kidney, the expression of PC2 is regulated by mir17 and RNA-binding protein Bicaudal C (114). However very little has been investigated in this aspect and certainly more studies are needed to demonstrate the involvement of microRNAs in the regulation of stress and pain. The small RNA and microRNA-mediated regulation of stress and pain might be of pharmacological interest also.

6.2. Changes in the novel PKCs-mediated signaling events

Stress and different forms of pain have strong effects on the peripheral and central nervous system through several neuro-chemical pathways. However, among all distinct pathways, activation of different PKCs, mostly atypical and/or novel PKCs (this group of PKCs are activated in a Ca^{2+}-independent manner) are the common pathways reported in several stress and pain conditions (21, 115-117). Interestingly, the activation of these novel PKCs in response to different stressors and types of pain correlates well at the behavioral level as well as the cellular level. For example, the level of PKCε increases in stress and pain (mechanical as well as thermal), and modulates NGF and mitogen activated protein kinases (MAP kinase)-mediated signaling events (117). Mechanical stress can also activate PKCδ and thus activate the Smad pathway in osteoblasts present in bone. This in turn enhances interleukin-11 (IL-11) expression and this may affect several other systems (116). Mechanical stress also induces sarcomere assembly which alters the morphology of cardiac muscles, a process where PKCs are involved (117). In the same notion, up-regulation and redistribution of PKCδ is observed in chronically hypoxic heart (115). PKC-mediated pathways are also involved in other stress signaling, such as oxidative stress.

6.3. Changes in the neuronal organization

Chronic stress induces transient plastic changes and may even induce long-term changes in the dendritic spine and neuronal patterns in the amygdala. For example, chronic unpredictable stress had little effect on CA3 pyramidal neurons and induced atrophy only in BLA-bipolar neurons (75-76). Thus chronic stress can induce contrasting patterns of dendritic remodeling in neurons of the amygdala and hippocampus. In addition the structures of neuronal ends and dendritic spines are altered. Even the distribution of neuronal ends in the peripheral tissue and spinal cord can be altered in response to stress/pain (22). Stress is known to induce synaptic changes. For example, stress-induced changes in synaptic connectivity have been shown in the neurons of the basolateral amygdala.

Stress and pain may have a role in “unsilencing of dendritic spines”, a mechanism by which activation of “silent synapse” can occur and result in activity- and sensory-dependent refinement of neuronal circuits. Silent spines are morphologically similar to other dendritic spines though these entities do not contribute to the total neuronal communications. Thus activation of silent spines can be one of the key phenomena involved in chronic manifestation of the stress and/or pain. This notion is supported by observations that β-estradiol, heat and mechanical pressure increase the neuronal output via

sensory neurons per unit area of the skin (118-119). However, further work is needed to confirm this.

7. TRPS AS DETECTORS AND MEDIATORS OF STRESS AND PAIN

As TRPs can be activated by different physical and endogenous chemical stimuli (Table 1), these channels have role in the regulation of several physiological and metabolic functions. The expression of TRPs is often tissues-specific which correlate well with the development and functions of specialized organs. Indeed, TRPs are critical elements that define the regulation, structure, development and function of certain organs, tissues and cells. For example, endogenous activity of TRPs are important for proper Ca^{2+}-signaling and functioning of brain, spinal cord, liver, immune cells, pancreatic cells, skin cells, keratinocytes, retinal cells, cardiac mayocytes, gut and many other specific organs and cells. So far several studies have confirmed (or indicated a strong correlation) that altered expression, function and/or regulation of TRPs are key changes which induce patho-physiological conditions like stress, neuropathic pain and cancer. For example, TRPV1 and TRPA1 participate in visceral hyperalgesia in chronic water avoidance stress (120). TRPM2 and TRPV4 are involved in oxidative stress-induced cell death of hippocampal neurons (121). TRPs are also involved in programmed death of different type of cells in response to stress-signaling. Rats exposed to chronic stress reveal reciprocal change in TRPV1 expression induced by corticosterone (122).

In a defined cellular system, TRPs mainly act as molecular detectors of stress- and pain-inducing stimuli (physical and chemical). TRPs also recognize several endogenous noxious compounds and their different metabolites that are often associated with the development of stress and pain (123). For example, a number of lipid derivatives can activate a battery of TRPs (Table 1). So far the effects of only limited lipid derivatives on few TRPs have been explored and the effect of the entire array of these lipid derivatives on all the TRPs remains untested. A better understanding of the effect of different lipid derivatives on all TRPs has medical and pharmacological importance. Apart from the lipid derivatives, several TRPs can also be activated by estrogen, endrogen, testosterone, cortisol and many other steroids (Table 1). In addition, the expressions of TRPs are often under the regulation of these steroids, neurotransmitters and neuropeptides (Table 1). These studies may explain why most of the steroids that are often used as pharmacological drugs exert side effects like pain and stress. Cholesterol, which may be up-regulated during stress, seems to have a regulatory effect on the function of TRPs too. This is due to the fact that most of the TRPs are located in the lipid raft regions (defined as cholesterol-rich lipid micro-domains) and function/behave differently when they are present in the lipid raft. In the same notion, recent studies confirmed that TRPs may have specific cholesterol-binding motif sequences and the cholesterol binding has regulatory roles on the ion channel properties (124-125). All this studies suggests that effects of neurotransmitters, neuropeptides, steroids and other noxious compounds on TRPs are relevant in the context of stress and pain and these effects are conserved to some extent throughout the evolution.

Activation of TRPs induces influx of Ca^{2+} and other cations. Thus TRPs act as mediators of different cellular signaling events and can have direct and opposite effects related to stress and pain. While the basal expression and endogenous activation of TRPs are involved in maintaining homeostasis for several ions, over-activation and constitutive inactivation seems to have major setbacks on the cellular system and are linked with the development of stress and pain. For example, over-stimulation of TRPs leads to an influx of excess Ca^{2+} which is generally associated with the cell death (126). Therefore deletion of certain cell types may have an adverse effect on tissue homeostasis. TRPs are also important for cellular uptake of Co, Fe, Ni and other important metal ions that are essential for several physiological and metabolic functions like bone formation, vitamin synthesis and maintenance of urine composition.

8. HOW TRPS REGULATE METABOLIC PATHOGENESIS IN STRESS AND PAIN?

TRPs are ubiquitously expressed in many tissues and cell types and have considerable functional and/or regulatory diversities. The distribution of TRPs in several tissues, like kidney, pancreas, and lungs is important for tissue specific metabolism and physiological functions. Recently, involvement of TRPs in different types of cancer and cancer pain has been demonstrated (127). As there are few reviews which already have addressed the involvement of TRPs in cancer, this review will not repeat the same. While cancer cells can certainly a factor for stress at the gross level, if secretion of noxious components from cancer cells are specifically regulated by and/or act on TRPs that remain to be explored. In addition to cancer, TRPs are regulated by a number of exogenous and endogenous components including several metabolic byproducts (Table 1). Therefore, misregulation of TRP's function leads to various pathophysiological disorders. Indeed, TRPs are involved in disorders like diabetes, obesity, dyslipidaemia, metabolic syndrome, atherosclerosis, metabolic bone diseases, male sterility and electrolyte disturbances which are linked with stress and pain (Figure 3) (128). TRPs are also involved in addiction and thus in behavioral responses. Therefore, the link between metabolic pathogenesis and the deregulation of TRPs are of pharmacological, clinical, social and economic importance as this will help to identify and develop potential means for better treatment (128). Here we discuss in detail the involvement of TRPs in metabolic disorders.

8.1. Involvement of TRPs in obesity

Whole genome scanning analysis for obesity genes implicated few TRPs, namely TRPC3, TRPC4, TRPM8, TRPP2, TRPML and TRPV6 which may play important roles in obesity (129). The best example of the involvement of TRPs in obesity was provided by TRPV1 and involvement of other TRPs in obesity needs further characterization. It has been reported that the consumption

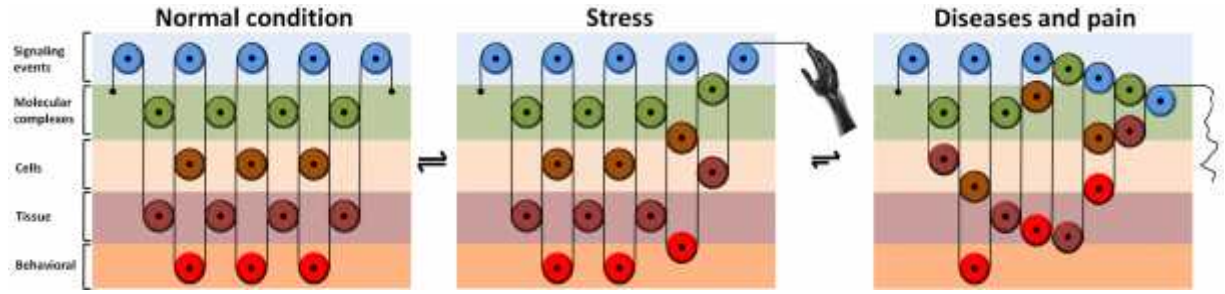

Figure 2. Stress is an altered state of mind and body which threatens biochemical and cellular balance, equilibrium and/or behavioral harmony which eventually disturbs the physiological, psychological and metabolic homeostasis of individual. Individual's function and behavior in stressed and painful conditions can be explained in terms of an organized set of signaling events controlled by cellular and molecular complexes. These can be best portrayed as multiple pulleys and levers connected to each other where each pulley denotes a key event essential at biochemical, cellular or tissue context. In stressed condition, the organized setup is challenged fully or partially but still remains functional. This setup may come back to its initial condition in absence of the prolonged and/or strong challenge. However, further challenges and stretching of the system results in an altered state where further adjustment is not possible. As a result of this prolonged stress and/or pain, the mind-body balance becomes minimum.

of chili in food increases the oxidation of fat present in adipose tissue of both mice and humans suggesting a potential role for TRPV1 in that process (130). Indeed, capsaicin decreases obesity in a dose-dependent manner by increasing oxidation of fat molecules (131). TRPV1 regulates food absorption, emesis, colitis and also regulates the gut - brain axis mainly by responding to endovanilloids and endocannabinoids (132-133). Pancreatic sensory nerves as well as pancreatic cells express TRPV1 and activation of TRPV1 induces preadipocyte differentiation, obesity-induced chronic inflammation and fat distribution (134-136). TRPV1-null mice are smaller and exhibit significantly greater thermogenic capacity compared to wild-type mice when supplemented with 11% fat diet (136). Interestingly, genetic deletion of TRPV1 is protective against obesity only in young animals. Aged TRPV1 knockout mice are more obese than their wild-type littermates (137). The reasons for this specific effect in the young stage are not clear. This probably indicates that factors, which are different in juvenile and adult stages, may control obesity through TRPV1. However, further studies are needed in this context.

The TRPV1-positive sensory nerves present in the intestine are activated by capsaicin and other spices and cause increased blood flow in intestinal region. This in turn reduces visceral adiposity but exerts very little effect on body weight (138). However the role of oral capsaicin on visceral adipogenesis is debatable as the oral capsaicin get metabolized before absorption from the gut lumen and thus very little remains available for circulation in adipose tissue (138). Capsaicin can also modulate energy balance and obesity by modulating signaling pathways. Recently, Kang *et al*. showed that capsaicin can suppress obesity-induced inflammation through nuclear factor (NF)-κB inactivation and/or PPAR-γ activation in the adipose tissues of obese mice (139). Taken together it suggests that TRPV1 and other TRPs are involved in food absorption and obesity regulation. These results are in agreement with the fact that in case of chronic stress, eating behavior is altered and appetite is reduced due to persistent high level of cortisol in circulating blood which activate the *ob* gene that causes obesity (140). Involvement of TRPV1 in obesity can also be explained by the crosstalk between TRPV1 with Cholecystokinin (CCK, released postprandially and elicits satiety signals) and the leptin (a circulating protein involved in the long-term regulation of food intake and body weight by inhibiting the food uptake) (141-144). Capsaicin-sensitive vagal primary afferents control the release of CCK. In reverse, leptin also affects capsaicin sensitive nerves. This feedback mechanism is supported by the fact that capsaicin stimulates electrical vagal nerve which in turn control the food intake and body mass (141). TRPV1 activation also blocks Leptin-CCK action, abolished the inhibitory effects of leptin and metabolic response to abdominal sepsis (142-144).

8.2. Involvement of TRP channels in diabetes mellitus

Diabetes mellitus is a life-style related metabolic disorder in which level of blood glucose, insulin secretion and insulin sensitivity are defective. Several TRP channels act as mediators of oxidative stress and have been associated with these disorders (126, 145). For example, TRPC, TRPV and TRPM channels are expressed in the pancreas and are involved in the regulation of insulin secretion and maintenance of Ca^{+2}-homeostasis (146). However, among all TRPs, TRPV1 seems to play an important role in diabetes. The TRPV1 containing sensory nerve fibres present in the pancreas regulate insulin secretion (147-148). Apart from the sensory nerve ending, TRPV1 is also present in islet β-cells, in the RIN and INS1 β-cell lines where activation of TRPV1 promotes insulin secretion by increasing Ca^{2+} concentration. Interestingly, either a TRPV1 inhibitor or EDTA (a Ca^{2+}-chelator) prevents this secretion (148). Secreted insulin binds to insulin receptors in the brain and TRPV1-positive sensory neuronal junctions and lowers the activation threshold of TRPV1. Subsequently, Ca^{2+}-influx mediated by TRPV1 induces local release of neuropeptides (e.g. substance-P, CGRP). In that context, recent studies have also shown that insulin not only sensitizes TRPV1 on sensory nerve endings but also increases the release of calcitonin gene-

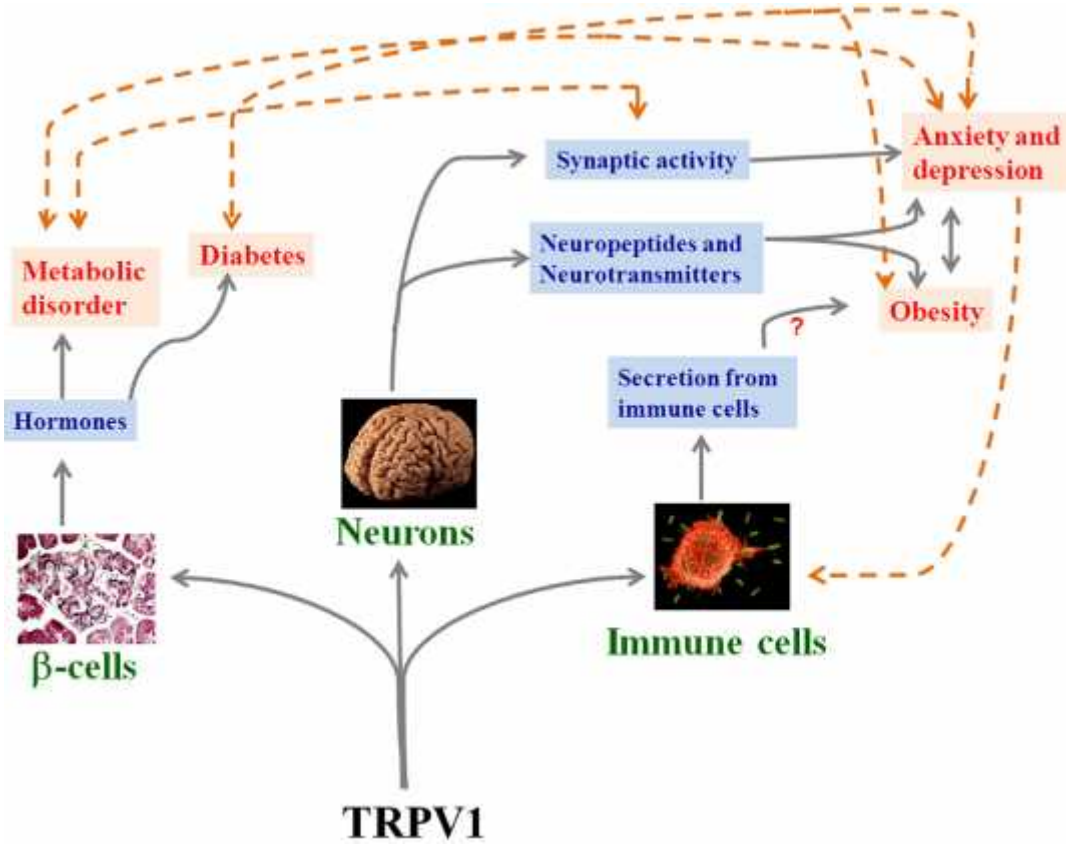

Figure 3. Involvement of TRP channels in stress. TRPV1, a member of TRP channel is present in different cells, like in neurons, pancreatic-β cells and immune cells. TRPV1 can regulate the secretion of neurotransmitters, neuropeptides, hormones, immnuochemicals and many other substances respectively. These substances in turn can induce altered synaptic activity, metabolic disorders, diabetes, obesity, anxiety, depression and many other physiological and psychological abnormalities relevant in stress and pain.

related peptide (CGRP) from pancreatic islets (149-150). The released CGRP provides a negative feedback regulation by reducing insulin release from islet β-cells. Razavi *et al.* demonstrated a pivotal role for TRPV1 in type-1 diabetes (151). In this case, T cell-mediated death of pancreatic β-cells results in insulin deficiency (152). TRPV1-positive sensory neurons in the pancreas also control islet inflammation and insulin resistance. It has been reported that elimination of these neurons in non-obese diabetic mice (NOD-mice) prevents insulitis and diabetes, despite systemic persistence of pathogenic T-cells (152). It seems that TRPV1 regulates insulin level in stressed condition and this regulation also involves cortisol and epinepherin, which are present in high-level in stressed conditions.

Apart from TRPV1, TRPV5 and TRPV6 are also involved in diabetes by regulating insulin secretion under the control of vitamin-D level (153). Earlier studies suggest that Vitamin-D is essential for normal insulin secretion and dietary intake of Ca^{+2} in pancreatic tissue. This is evident as insulin secretion is impaired in vitamin D-deficient rats but can be restored by 1,25 (OH)2D3 supplementation because the expression of TRPV5 and TRPV6 is low in case of vitamin-D deficient rat (153). In a similar manner, TRPM2 is activated by hydrogen peroxide causing Ca^{2+}-influx and thereby regulating insulin secretion in rodent and human β-cells (154- 155). TRPM3 also regulates β-cell activity in response to steroids (156). However, detailed research is required to elucidate how these TRPs regulate insulin secretion and determine their roles in the pathogenesis of diabetes.

8.3. Involvement of TRPs in addiction and neuropathy

TRPs are extensively involved in alcoholism, smoking and other addictions which are life-style and stress-related phenomena that lead to several metabolic changes subsequently. Consumption of alcohol is a chronic and clinical problem that gives rise to several physiological manifestations like liver disease, pancreatitis, gastrointestinal and neurological disorder e.g. polyneuropathies which are common in alcohol addicted patients (157). Ethanol-induced peripheral neuropathy develops in as many as 48% of chronic alcoholics and often involves the development of painful hyperalgesia via mechanisms that are largely unclear (158-160). Interestingly, TRPs seem to be involved in these addictions and alter the state of physiology by several mechanisms.

Endogenous TRPs are also present in various parts of the brain, namely in substantia nigra, hippocampal pyramidal neurons, hypothalamus, brainstem and cortex (83-86). These endogenous TRPs can affect the HPA-axis and thus may account for these addictions. TRPs share a functional cross talk with other receptors including opioid receptors that are involved in addiction. For example, blockade of opioid receptor affects the processing of thermal stimuli by neurons (161).

Interestingly, some of addictive agents directly activate TRPs at pharmacological concentrations. For example, ethanol can directly activate as well as potentiates TRPV1 (162). In the presence of ethanol the threshold for heat activation of TRPV1 decreases from 42°C to 34°C, at which spontaneous activation of TRPV1 can occur in the tongue and skin (163). Other TRPs are also involved in the development of addictive behavior. For example, TRPM8 is also involved in ethanol-induced behavioral response (164). TRPs are also involved in nicotine addiction (165). Interestingly, the effect of nicotine on TRPs seems to be conserved throughout the animal kingdom. Xu *et al.* showed that the TRP1 and TRP2 in *C. elegans* are involved in nicotine sensitivity (166). Similarly, Nilius *et al.* also showed that nicotine directly activates TRPA1 (167). These studies may explain why nicotine patches produce some burning sensation, itching and skin irritation.

Alcoholism apparently changes lipid metabolism and signaling events via opioid receptors, μ-opioid receptors and other TRPs which in turn modulates the synaptic structure and functions leading to ethanol-induced metabolic disorders (168). Indeed, regular ethanol uptake increases the levels of endocannabinoids in brain, decreases AEA (169-170) and the expression of CB1 receptors during chronic ethanol-induced dependence and withdrawal (171). Thus it is possible that addictive ethanol intake modulates the endocannabinoid levels which in turn alter the behavior through actions on both CB1 and TRPV1. It was also reported that the μ-opioid receptor (MOP) agonist morphine can inhibit ethanol-activated TRPV1 responses by decreasing cAMP-dependent PKA pathway (172). However, recent studies indicate that potentiation of TRPV1 by ethanol can modulate the PIP_2 interaction with TRPV1 and this potentiation is not sensitive to opioids (173). Consistent with these observations, TRPM8 reveals less ionic conductance in response to ethanol by regulating the PIP_2 interaction with TRPM8 (164). How ethanol, nicotine and other addictives modulate different TRPs requires more studies and these studies may help to further understand addiction and other related physiological problems.

Progress has also been made to understand the role of TRPs in chemotherapy-induced neuropathy. This is particularly important for cancer treatment where Taxol, a microtubule stabilizer-based drug is routinely used as a life-saving chemotherapeutic agent. Why administration of Taxol produces strong neuropathy including other psychological and physical stress is not clear (174). However, TRPs, especially TRPV1 and TRPV4 seem to be involved in this Taxol-induced neuropathy. For example, administration of TRPV4-specific antisense oligodeoxynucleotides to the spinal cord reduces the expression of TRPV4 in sensory nerves and also abolishes Taxol-induced mechanical hyperalgesia and attenuates hypotonic hyperalgesia by 42% (175). This indicates that TRPV4 is involved if not essential in Taxol-induced neuropathic pain. This is in full agreement with the fact that TRPV4 and TRPV1 interacts with polymerized microtubules and with soluble tubulin dimer by their C-terminal cytoplasmic region (176). Though the exact mechanism is not clear, TRPV-tubulin complexes seem to be involved in multiple signaling events including neuropathy. Further detailed studies are required to clarify this aspect.

8.4. Involvement of TRPs in ageing

Aging is influenced by complex factors such as circumstances, living habits and genetic backgrounds. Though the exact molecular mechanism of aging has not been elucidated yet, premature aging has been considered as a stress-related problem. Recent studies have pointed that TRPs are involved in the aging process by several means. In case of chronic stress, endogenous corticosteroid level is high and the expression of respective receptor is low. This results in imbalance in Ca^{+2}-homeostasis and causes ageing of hippocampous neuron, a process where involvement of TRPs is plausible. Similarly, the ageing of human skin is induced by both intrinsic ageing and photo-ageing processes (176-177). It has been reported that TRPV1 channels play an important role in heat shock-induced MMP-1 expression in human keratinocytes in which the expression of some matrix metalloproteinases (MMPs) is up-regulated (178-179). Enhanced MMPs cause degradation of dermal collagen during UV-induced photo-ageing.

TRPs are also involved in aging process by regulating the anti-aging hormone, namely Klotho, a type I membrane glycoprotein. The extracellular domain of Klotho has two tandem copies of a β-glucuronidase-like sequence, which can be released as soluble factor after cleaved by metalloproteinases such as ADAM10 and ADAM17 (180). It has been demonstrated that Klotho regulates TRPV5 (181). The α-Klotho co-localizes with TRPV5 in the distal convoluted tubule in the kidney. Moreover, Ca^{2+}-uptake is increased in cells that are positive for both TRPV5 and Klotho as compared to cells that express only TRPV5. Interestingly, sugar residues seem to be important for TRPV5 activation. This is evident by the fact that salicydase, endo-F or Klotho treatment results in the activation of TRPV5 (181). Extracellular soluble Klotho induces deglycosylation of TRPV5. This retains TRPV5 at the plasma membrane for a longer time and also prevents its recycling. Therefore Klotho not only stimulates TRPV5 but also accumulates more TRPV5 in the plasma membrane. In agreement with the regulation of TRPV5 by Klotho, age-related disorders are observed in many TRPV5 expressing tissues like kidney, lung, bone, gastric wall and in the skin of Klotho knockout mice. It remains to be explored whether other TRPs are also involved in the aging process.

8.4. Involvement of TRPs in male sterility

It is well known that emotional and psychological stress has deleterious effect on reproductive abilities and results in decreased conception (182-183). But how stress actually modulates these aspects are not clear. Recent studies indicate that TRPs are involved in this process. So far several TRPs have been detected in the spermatozoa and in mature sperm cells. Notably, the localization of TRPs in the sperm cells is conserved throughout the evolution and thus somewhat functionally important. The involvement of TRPs in the sperm motility and fertility seem to be important as these channels allow Ca^{2+}-influx. In *Drosophila*, TRPC homolog (TRP-3) is present in intracellular vesicles of spermatids and after activation these vesicles translocate to the cell membrane (184). In human sperm cells, TRPV1 is located in the post-acrosomal area and in the mid-piece (185). In addition, several endogenous stimulators have been identified in the seminal plasma and other reproductive fluids. For example, N-acylethanolamides (NAEs) and lipid derivatives able to activate TRPs are present in seminal plasma as well as in other reproductive fluids (186). There are several other endogenous lipid ligands like arachidonylethanolamide (AEA; also known as anandamide), palmitoylethanolamide (PEA), and oleoylethanolamide (OEA) that are present in seminal plasma and oviductal fluid and can therefore regulate the localization of the TRPV1 in sperm cells (187). Activities of TRPs seem to be important for the sperm acrosomal reaction as inhibition of TRPV1 inhibits sperm fusion with oocytes (185). Excess production of reactive oxygen species (ROS) (a condition relevant in oxidative stress situations when superoxide anion, hydroxyl radical, nitric oxide, peroxides, and peroxynitrile are produced more and/or antioxidant enzymes are insufficient) can also exert deleterious effect on sperm cells via TRPs (188-189). In normal conditions, ROS have an important physiological role and are required for sperm capacitation and acrosomal reaction. Excess ROS generation may results in immature and abnormal spermatozoa leading to male sterility.

9. CONCLUSION AND FUTURE OUTLOOK

In the last few years' significant progress has been made in understanding pain and stress at the molecular, cellular, psychological and behavioral level. Interestingly, both stress and pain seem to have a shared evolutionary origin as these processes help individuals to avoid unpleasant environments and cope better with different adverse situations. Ultimately, this leads to better adaptation. As stress and pain are complex disorders having environmental, genetic, physical and/or psychological backgrounds, a more "tailor-made" approach to cure stress and pain is required. It is relevant to mention here that so far there is no effective and tailor-made treatment available for stress and/or chronic pain (1). In this context, meditation and mental capacity to cultivate positive emotion seems to activate certain neuronal circuitries which may prove helpful. For example, it has also been demonstrated that zen practitioners display a reduced duration of neural responses linked to certain functions (190). In a similar manner, central and autonomic nervous system interactions are also altered by short-term meditation (191).

Tough the present understanding of how TRPs are involved in different forms of stress and pain are just at their beginning stage, involvement of TRPs in stress and pain has gained tremendous medical attention. This is mainly due to the fact that TRPs represent key yet diverse pharmacological targets which can be useful to treat different forms of stress and pain in a systematic manner. At presently very little is known about the identity of different endogenous small molecules that can either act as modulators of these TRPs or are secreted due to activation of TRPs. Also how these components and their derivatives act on and modulate arrays of TRPs remains to be characterized. The fact that certain TRPs can be modulated by physical stimuli like temperature, mechanical pressure, osmolarity and different odors gives hope that certain form of stress and pain can be cured by physical stimuli without the use of chemical agents (**192**). This is particularly fascinating as TRPs can modulate the HPA-axis at the upstream as well as the downstream direction. Indeed, commonly practiced analgesic, anxiety- and stress-removal methods like meditation, body massage, acupuncture, water and music therapy, etc most likely to affect the HPA-axis via modulating relevant TRPs in the peripheral tissues (**193**). For example, it has been shown that activation of TRPV1 in the brain contributes to the analgesic effect of acetaminophen. However, more studies are needed to and future research should address to explore these possibilities.

10. ACKNOWLEDGEMENT

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Abbreviations: ACTH: Adrenocorticotrophic Hormone, BDNF: Brain-derived neurotrophic factor, CBP: Chronic back pain,CCK: Cholecystokinin, CGRP: Calcitonin gene-related peptide, CRH: Corticotrophin-Releasing Hormone, EGF: Epidermal Growth Factor, GABA: γ-Aminobutyric acid, GC: Glucocorticoid, HDLC: High Density Lipoprotein Cholesterol, HPA axis: Hypothalamic-Pituitary-Adrenal axis, LTD: Long Term Depression, LTP: Long Term Potentiation, MRI: Magnetic Resonance Imaging, NGF: Nerve Growth Factor, NOD-mice: Non-Obese Diabetic mice, NPY: Neuropeptide Y, PAR2: Protease Activated Receptor, PKC: Protein Kinase C, SP: Substance-P, TPC: Total Plasma Cholesterol, TRPs: Transient Receptor Potential channels, TRPV: Transient Receptor Potential Vanilloid

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