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Review article

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SOCIAL STRESS ADAPTS SIGNALING PATHWAYS INVOLVED IN STIMULATION OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

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In socially organized mammals the predominating stressors are not physical events but arise from the immediate social environment of the animal. Crowding typically evokes social stress reactions with prominent psychosocial components mimicking emotional state alterations. Depending on the nature, intensity and duration of the initial stimuli, they can either reduce or increase the response of the hypothalamic-pituitary adrenal (HPA) axis. In homologous desensitization only stimulation by desensitizing hormone is attenuated, in heterologous desensitization diminished responsiveness to additional activators occurs. Social stress of crowding (21 rats in a cage for 7) for 3, 7, 14 and 21 days considerably reduced the corticosterone response to intracerebroventricular (icv) administration of carbachol, a cholinergic muscarinic receptor agonist due to a homologous desensitization and down-regulation of central muscarinic receptors by an increased secretion of acetylcholine. Crowding stress significantly reduced the HPA response to icv isoprenaline, a β-adrenergic agonist and clonidine, an α_2-adrenergic agonist and only moderately diminished the response to phenylephrine — an α_1-adrenergic agonist. The stimulatory effect of dimaprit, a nonselective histamine H_2-receptor agonist on HPA axis was considerably impaired in crowded rats while the response to 2-pyridylethylamine, a H_1-receptor agonist was moderately affected. Social crowding stress did not substantially alter the CRH-induced ACTH and corticosterone response while it suppressed the vasopressin-induced responses. Indomethacin did not change basal plasma ACTH and corticosterone levels, indicating that prostaglandins are not involved in basal regulation of the HPA activity. Inhibition of prostaglandins synthesis by indomethacin significantly diminished the vasopressin-induced HPA response under both basal and social stress conditions, whereas it did affect the CRH-elicited HPA stimulation under both these circumstances. Social stress inhibits the nitric oxide effect on the CRH-induced ACTH response but it does not alter the AVP-induced responses. These results indicate a specific and distinct influences of social crowding stress on the neurotransmitters- neurohormones- prostaglandins- and nitric oxide-induced HPA responses.

Key words: *social crowding stress, adaptation, HPA response, neurotransmitters, neurohormones, prostaglandins, nitric oxide.*

INTRODUCTION

Man and animals have physiological and psychological mechanisms that are activated in dangerous situations (1). Any actual or perceived threat to homeostasis or expectations of an organism initiates a series of central nervous system mediated, adaptive behavioural, autonomic and neuroendocrine responses (2, 3). In general, stress responses result from coordinated activation of several effector systems, including the sympathoneural and sympathoadrenal system as well as the hypothalamic-pituitary-adrenal (HPA) axis (4—6).

The majority of our current informations on the stimulation of the central stress responsive systems or some state of stress pathology is derived from animal reactions to various kinds of physical stressors e.g. restraint, electric foot-shocks, cold stress, noise. Many of these procedures bear little or no relation to the environmental challenges experienced by an animal (7). In socially organized mammals, however, the predominating stressors are not physical events but arise from the immediate social environment of the animal and psychosocial conflicts (8).

Physiological stress is caused by strong physical or environmental changes treatening internal homeostasis, whereas psychosocial or psychological stress is evoked by subjective perception and cognitive processes that control the behavioral interactions of the group members and determine their relationships. Crowding typically induces social stress reactions with prominent psychosocial components and mimicking emotional state alterations. Social interactions have a profound influence on neuroendocrine functions in mammals (9, 10).

Psychosocial stimuli act through higher nervous processes which trigger the release of glucocorticoids and catecholamines into the blood stream. During chronic social stress there is no single, unique response by the animal, but a highly complex set of neuroendocrine changes, which are dependent on the interaction between situational factors and individual characteristics of the animal. Psychological stress, like a variety of stressful stimuli cause marked increases in neurotransmitters release in brain structures, preferentially in the hypothalamus, amygdala and locus coeruleus regions (11). The monoaminergic neurotransmitters e.g. catecholamines, histamine, serotonin and acetylcholine are significantly involved in the synthesis and release of hypophysiotropic hormones by neurons in the hypothalamus, and ACTH from anterior pituitary corticotrophs (12—14). Neurotransmitters and hypothalamic corticotropin releasing hormone (CRH) and vasopressin (AVP) activate the pituitary-adrenal system and stimulate adrenal glucocorticoid secretion. Most forms of stress considerably and in different way alter the brain monoaminergic neuronal and hypothalamic CRH and AVP activity by their enhanced synthesis or release.

The effect of social stress on the hypothalamic-pituitary-adrenal system responses to neurotransmitters and neuropeptides, CRH and AVP, has not been elucidated yet.

TOLERANCE, ADAPTATION, DESENSITIZATION

It is well known that an initial exposure of the hypothalamic-pituitary-adrenal axis to a stressor can alter the response of this axis to the same, as well as other, noxious signals (15, 16). Daily exposure of the animals to the same stressors reduces the pituitary-adrenal response to the stimulus. Tolerance, subsensitivity, adaptation or desensitization refers to the situation in which repeated exposure to the same stimulus elicits a diminishing effect on ACTH and corticosterone secretion and appears to be due to diminished emotional arousal evoked by the stimulus (17, 18). Desensitization is a common property of virtually all membrane receptors and is the process by which receptors are inactivated in the prolonged presence of agonist.

Homologous or specific desensitization is characterized by the fact that only stimulation by the desensitizing hormone is attenuated. Homologous desensitization appears to occur in response to nearly all hormones that stimulate or inhibit adenylate cyclase. Homologous hormone induced decrease in adenylate cyclase activity occurs rapidly and reversibly. In homologous desensitization uncoupling of receptor-adenylate cyclase and sequestration of receptors from the cell surface is involved in the subsensitivity (19).

In contrast, *heterologous desensitization* is characterized by a diminished responsiveness to additional hormones and to other activators of adenylate cyclase. Heterologous desensitization is not associated with receptor sequestration or down-regulation but instead involves a functional uncoupling of the receptors and other components of the adenylate cyclase system (20).

On the other hand, repeated exposures to relative intense stimuli or persistent stress regimen may induce a state of *sensitization*, marked by stronger response of hormone release than was initially observed (21, 22).

NEUROTRANSMITTER SYSTEMS ADAPTATION DURING CROWDING

A. Cholinergic Muscarinic System Adaptation

In the brain acetylcholine (ACh), a major central and peripheral autonomic neurotransmitter, is one of the neurotransmitters clearly involved in the stimulation of hypothalamic release of CRH (23). Acute stress of immobilization increases the synthesis, binding and release of ACh in the

hippocampus and limbic structures (24). Chronic stress induces adaptive changes in cholinergic terminals expressed as a reduction of the choline uptake and an increase in the number of muscarinic binding sites in the septo-hippocampal cholinergic system which is involved in the pituitary-adrenal response to stressful stimuli (25). We found that social stress of crowding (21 rats in a cage for 7) for 3, 7, 14 and 21 days considerably reduces the increase in serum corticosterone level induced by intracerebroventricular (icv) administration of carbachol a cholinergic muscarinic receptor agonist (26—28). Acute and chronic stress cause an increase in ACh release and compensatory down-regulation of muscarinic receptors. The reduced responsiveness of the HPA axis during crowding stress may be elicited by a homologous desensitization and down-regulation of hypothalamic and/or anterior pituitary muscarinic receptors (29) following an increased secretion of ACh. Although icv carbachol stimulates the release of CRH from hypothalamic paraventricular nucleus, CRH receptors on anterior pituitary corticotrophs retain their reseponsiveness to CRH during crowding stress (27, 28). Muscarinic acetylcholine receptors coupled to phospholipase C (PLC) desensitize by both homologous and heterologous mechanism and modulation of the activity of protein kinase (PKC) can affect the development of desensitization. Homologous desensitization of muscarinic receptor may be regulated by β-adrenergic receptor-like kinase, while phosphorylation by protein kinase C (PKC) or cAMP- dependent protein kinase may regulate heterologous desensitization of the muscarinic receptor during social crowding stress (20).

B. Adrenergic System Adaptation

Adaptive changes induced by psychological stress include monoaminergic systems. Repeated or chronic stress increases the release of brain catecholamines and their chronic availability elicites reduction in the density and desensitization of β-adrenoceptors in several regions of the brain (30). This is considered one of the biochemical mechanisms in receptor adaptation in order to prevent some dangerous effects of the persisting stress-induced high levels of catecholamines.

Crowding stress for 3—7 days considerably reduces the rise in serum corticosterone elicited by icv administration of isoprenaline, a β-adrenergic receptor agonist and clonidine, an α_2-adrenergic agonist. However, crowding diminishes to a lesser extent the increase in serum corticosterone evoked by icv phenylephrine, an α_1-adrenergic agonist (13, 31). Adrenergic β- receptors, like cholinergic muscarinic receptors are linked to stimulatory G-proteins to stimulate adenyl cyclase and are regulated by phosphorylation which is obligatory for desensitization of receptors to their agonists. Phosphorylation of

the β-adrenergic receptor by cAMP dependent kinase and PKC during stress is intimately involved in the desensitization of the receptor.

Receptors are not lost during short-term desensitization since receptor function restores rapidly after removal of agonist. Long-term exposure to agonist down-regulates receptor expression for many G protein-coupled receptors. In the presence of noradrenaline which stimulates α_2-receptors, these receptors down regulated to about 50%. The down-regulation of the α_2-adrenergic receptors *in vitro* is evoked by an increase in the rate of receptors degradation since their density decreases for a prolonged period of time (32). Increased release of noradrenaline during crowding stress may decrease α_2-adrenergic receptor density and markedly diminish the stimulatory effect of clonidine on corticosterone secretion (31). Crowding stress does not significantly affect the pituitary-adrenocortical response stimulated *via* α_1-adrenergic receptors which couple to a distinct class of G proteins to activate production of the second messengers inositol triphosphate and diacylglycerol.

C. Histaminergic System Adaptation

Histamine seems indispensable to the normal functioning of the central nervous system and the HPA axis (33). Histamine-immunoreactive neuronal fibres and terminals are most numerous in different hypothalamic nuclei (34). Histamine and its central receptors are known to induce or mediate the HPA response (35, 36). Different kinds of stressors affect central histamine receptors as well as the synthesis and turnover of histamine. It is generally accepted that the histaminergic systems modulate the HPA axis, predominantly through stimulation of the hypothalamic release of CRH (37).

Social crowding stress applied for 3, 7 and 14 days, markedly though insignificantly, diminished the corticosterone response to pyridylethylamine (PEA), a histamine H_1-receptor agonist measured 1h after administration. On the other hand crowding stress caused a highly significant impairment of the corticosterone response to dimaprit, a histamine H_2-receptor agonist (38) and a moderate H_3 receptor antagonist (39). A maximum decrement of dimaprit-induced response was observed after 3 days and gradually fell down after 14 days of crowding (28, 40).

Dramatic impairment by chronic social crowding stress of the responsiveness of the HPA axis to histamine H_2-receptor stimulation is comparable, regarding its time-course and intensity, to a similar reduction in the corticosterone response to β-adrenergic and cholinergic muscarinic receptor stimulation in crowded rats (26). Signal transduction through histamine H_2-receptors, like that through β-adrenergic receptors, appears to involve primarily the adenylate cyclase pathaway (41). Our results suggest that

impairment of this second messenger system may be mainly responsible for the dramatic reduction of the corticosterone secretion after icv administration of dimaprit.

Histamine H_1-receptors which utylize the phosphatidylinositol and protein kinase C system for stimulation transduction (42, 43) are fairly resistant to desensitization during crowding stress. Histamine H_1-receptors may be desensitized by both homologous and heterologous mechanisms since an increased synthesis, release and turnover of histamine and other biogenic amines under different stress conditions are well known. Although desensitization of the histamine H_1-receptor-mediated inositol phoshate accumulation was found in the guinea-pig cerebral cortex slices and intestinal longitudinal smooth muscle (44), the H_1 agonist-induced desensitization of inositol phosphate production was not characterized in complex central nervous system structures. Thus our results suggest the prevalence of desensitization of the adenylate cyclase system during chronic social stress, as was demonstrated in other chronic stress models.

In conclusion, the present data show that social crowding stress considerably reduces the responsiveness of the HPA axis to adrenergic, muscarinic cholinergic and histaminergic stimulation, and that this reduction seems to be caused mainly by the functional desensitization of central adrenregic α_2- and β-receptors, muscarinic receptors, and histamine H_2-receptors.

CRH- AND AVP-INDUCED HPA RESPONSES DURING CROWDING

CRH is generally considered the primary and most potent activator of the pituitary-adrenal axis (12). Arginine vasopressin, the first identified secretagogue of ACTH, also coregulates ACTH secretion from pituitary (45). AVP has intrinsic capacity to stimulate ACTH secretion, and potentiates the stimulatory effects of CRH. These ACTH-secretagogues are synthesized in the hypothalamic paraventricular nucleus (PVN), by cell bodies of parvocellular neurosecretory neurons that project to the zona externa of the median eminence. These neuropeptides are released by stress signals from their stores to the hypophyseal portal system and induce the release of ACTH from the anterior pituitary corticotrops. In turn, ACTH stimulates the secretion of corticosterone from the adrenal cortex.

In normal rats, AVP is colocalized in approximately half of the CRH positive parvocellular neurons and these neurons are the main source of AVP in the hypophysial portal blood. The other half of the CRH axons contain little or no detectable AVP (46). Differential activation of these subpopulations of CRH axons could provide a mechanism regulating independently levels of CRH and AVP in portal plasma. Although single and repeated exposure of rats to immobilization stress can significantly upregulate the AVP as well as the

CRH mRNA generation in the hypothalamic CRH neurosecretory system (47), in stressed rats the number of AVP-expressing parvicellular CRH neurons increases more potently than AVP-deficent CRH neurons (48—50). Also chronic psychosocial stress increases the AVP, but not the CRH, content in the zona externa of median eminence (51). During chronic stress pituitary AVP receptor regulation is involved in the adaptation of the HPA axis (52). The activation of the HPA axis is characterized by expression of messenger RNA and CRH synthesis and release from isolated rat hypothalamus and is activated by a major intracellular signaling system, cAMP and the cAMP-dependent protein kinase A (PKA). AVP and CRH bind to specific pituitary corticotrop membrane receptors which activate different second messengers. The rat pituitary AVP receptor subtype V1b is coupled to phospholipase C and phosphoinositide-protein kinase C (PKC) pathway which plays a crucial role in the stimulatory action of AVP on adenohypophyseal cells. The CRH receptor is coupled to an adenylate cyclase (53).

Repeated stress induces rapid adaptation of the CRH mRNA response and desensitization of the pituitary ACTH response, which may be caused by negative feedback mechanisms, as well as depletion of the releasable ACTH pool, or down-regulation of pituitary CRH receptors (17). Chronic social stress can alter levels of CRH and AVP mRNA in rat brain (54).

In rats crowded for 3 days we found that the ACTH response to CRH is somewhat facilitated and corticosterone response remains unaffected indicating that the HPA system is fully sensitive or even hyperactive. This may reflect predominantly a moderate up-regulation of pituitary CRH receptors. By contrast, crowding stress considerably reduces the AVP-induced ACTH and corticosterone response (55, 56). This may result from desensitization and/or a decrease in the number of AVP receptors in the anterior pituitary corticotrops, or from desensitization of the AVP-stimulated intracellular inositol triphosphate and the PKC signaling pathway.

AVP plays a primary role in the regulation of the pituitary adrenal axis during adaptation to stress (50, 52). Chronic stress increases the expression of AVP in parvicellular neurons of the PVN, and AVP but not CRH secretion into the pituitary portal circulation. Changes in density and sensitivity of pituitary AVP receptors seem to play a major role in adaptation of the HPA axis to crowding stress.

PROSTAGLANDINS IN CRH- AND AVP- INDUCED HPA RESPONSES DURING CROWDING

The stimulatory action of CRH and AVP on the anterior pituitary corticotrop receptors depends on and may be modulated by different neuromodulators including prostaglandins (PGs). They mediate the HPA

responses to neurotransmitters involved in regulation of this system (57—60). Brain prostaglandins evidently mediate the interleukin IL-1β—induced ACTH secretion (61, 62). Prostaglandins stimulate the release of ACTH from the anterior pituitary corticotrops either directly or by the hypothalamic release of CRH and/or AVP and they can directly stimulate steroidogenesis in rat adrenal glands (63).

Prostaglandins are known to be released under stressful circumstances. They mediate responses to psychological stress, including the ACTH and corticosterone response (64). Our results indicate that in rats crowded for 3 days or in nonstressed animals PGs are not involved in the pituitary-adrenocortical response elicited by direct homologous stimulation of pituitary CRH receptors by intraperitoneal administration of CRH. On the other hand, PGs significantly mediate the stimulatory action of AVP on the HPA axis, under basal circumstances and both the hypothalamus and the anterior pituitary may be involved in this interaction. Social crowding stress does not affect the significant participation of the PGs system in the transduction of AVP hypophysiotropic signals found in nonstressed animals (64). Therefore, PGs play a distinct role in stimulation and adaptation of the CRH and the AVP regulatory systems under basal and social stress conditions.

NITRIC OXIDE IN CRH- AND AVP- INDUCED HPA RESPONSES DURING CROWDING

Nitric oxide (NO) acts as a neuronal messenger in the central and peripheral nervous system (65). Nitric oxide is enzymatically synthesized from L-arginine through the action of either constitutive or inducible NO synthase isoforms. Of the isozymes of NO synthase (NOS), the neuronal type (nNOS) is widely distributed in the brain. A NOS-like activity and NOS mRNA are present within the key structures of the HPA axis including parvocellular division of the hypothalamic PVN and in a subpopulation of CRH- and AVP-expressing neurons (66—68). To date, there has been no demonstration of NOS within the corticotrops. Nitric oxide acts as a neuromodulator in the hypothalamic-pituitary adrenal axis (HPA).

Under basal conditions endogenous NO is not activated to substantially affect the resting HPA activity. Different stressors augment NOS expression in key structures of the HPA axis. Acute immobilization stress causes the up-regulation of expression of neuronal nitric oxide synthase (69), the enzyme which plays a major role in NO biosynthesis in the neuroendocrine system. Blockade of NO synthesis significantly impairs ACTH release in response to a mild electroshock and water avoidance stress (70).

In stressed rats NO synthase blocker L-NNA totally abolishes the CRH-induced increase in ACTH secretion and slightly diminishes the corticosterone response compared with stressed saline-treated controls (56). This suggests that either social stress abolishes the action of endogenous NO on the CRH-induced ACTH response, or L-NNA does not affect the synthesis of endogenous NO in chronically crowded rats.

Nitric oxide may also influence synthesis or release of neurotransmitters such as catecholamines and prostaglandins which are involved in the control of HPA activity (65). The increase in the CRH- and AVP-induced secretion elicited by the NOS blocker may be partly connected with changes in activity of hypothalamic dopamine and noradrenaline which are known to activate the HPA axis (71). Although central α_1 and β-adrenergic receptors are also moderately involved in CRH- and AVP-induced increase in corticosterone sectetion, respectively, (72) hypothalamic adrenergic mechanism does not seem to play a major role in the NO-induced changes in ACTH and corticosterone secretion. Nitric oxide may modify the HPA response to CRH and AVP via an interaction with a cyclooxygenase pathway. NO may indirectly stimulate or reduce cyclooxygenases and subsequently increase or inhibit the synthesis of prostaglandins in different tissues, including brain structures involved in regulation of the HPA activity. Our results show that crowding stress does not affect the potent stimulatory effect of NOS blocker on the AVP-induced ACTH response, but it abolishes the stimulatory action of L-NNA on the CRH-evoked ACTH response. These findings indicate that social stress desensitizes the mechanism of action of NO in the CRH- but not the AVP-induced ACTH response. They also indicate that endogenous NO may separately modulate the CRH- and AVP-induced stimulatory pathways in the HPA axis stress response.

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