Overview

IN SEARCH OF CONCOMITANT ALTERATIONS OF DOPAMINERGIC AND NEUROTENSINERGIC SYSTEMS IN STRESS CONDITIONS

Georgina Rodríguez de Lores Arnaiz

Marta C. Antonelli

Instituto de Biología Celular y Neurociencias "Prof. E. De Robertis", CONICET-UBA, Facultad de Medicina, Universidad de Buenos Aires, Paraguay 2155, 1121-Buenos Aires, Argentina.

G. Rodríguez de Lores Arnaiz (corresponding author). Instituto de Biología Celular y Neurociencias "Prof. E. De Robertis" CONICET-UBA, Facultad de Medicina, Universidad de Buenos Aires, Paraguay 2155, 1121-Buenos Aires, Argentina. E-mail address: grodrig@ffyb.uba.ar

Telephone: 54-11-5950-9626. FAX: 54-11-4508-5341.

Abstract

The aim of the present article is to review experimental evidence which suggest joint involvement of both the dopaminergic and neurotensinergic systems in stress conditions. At present, the concept of stress refers to an environmental demand exceeding the normal regulatory ability of an organism, particularly during unpredictable and uncontrollable situations. Chronic stress yields devastating effects including cognitive and working memory dysfunctions, for which neurotransmission mediated by the catecholamines dopamine and noradrenaline is crucial. Catecholamine synthesis depends on the rate-limiting enzyme, tyrosine hydroxylase, whose expression is associated with working memory and the response to chronic stress. Neurotensin is a tridecapeptide widely distributed in the nervous system, at both central and peripheral levels, which behaves as a neurotransmitter or neuromodulator. It mediates diverse biological actions including reward, locomotion, pain modulation and stress. Neurotensin and its high affinity NTS1 receptor are densely localized in areas that process emotion (amygdala nucleus), cognition (such as hippocampal nuclei and cortical areas) and the response to stress (hypothalamic nucleus). Experimental evidence indicates a crosstalk between the dopaminergic and the neurotensinergic systems either from an anatomical or a biochemical point of view. It is suggested that a concomitant alteration of dopaminergic and neurotensinergic systems takes place in diverse stress conditions.

Keywords Dopamine - Dopaminergic System- Tyrosine hydroxylase - Dopaminergic D2 Receptor - Neurotensin -Neurotensinergic System- NTS1 Receptor - Stress

Abbreviations

HPA: Hypothalamic-pituitary-adrenal

ACTH: Adrenocorticotropic hormone

TH: Tyrosine hydroxylase

GPCRs: G-protein-coupled receptors

Table of contents

This review is far from exhaustive but rather is intended to highlight specific issues with attention placed on the relation between dopamine and neurotensin in the stress condition. Under each subheading, the reader is directed to a few selected original articles as well as to complete review articles.

Literature regarding interactions in functioning of dopaminergic and neurotensinergic systems is abundant and the reader may consult very well documented and extensive reviews. The aim of the present article is to review experimental evidence which suggests joint involvement of both the dopaminergic system and neurotensinergic systems in stress conditions.

Basic concepts of stress

The most recent revised concept of stress has been defined as "*any environmental demand that exceeds the physiological regulatory capacity of an organism"*[1], particularly "*during situations of unpredictability and uncontrollability"* [2]. The major neuroendocrine and physiological stress response to a threat from a dangerous situation that triggers the 'fight-or-flight' response is the activation of the hypothalamic-pituitary-adrenal (HPA) axis. Activation of the HPA axis is triggered by corticotrophin releasing factor in the paraventricular nucleus that induces adrenocorticotropic hormone (ACTH) release from the pituitary, which in turn releases glucocorticoids from the adrenal. The end product of HPA axis activation (i.e. the release of glucocorticoids by the adrenal gland) serves to alert an organism to environmental and physiological changes and to maintain homeostasis [3]. However, another core neuroendocrine response to stressful stimuli is the activation of the autonomic nervous system, which results in a rapid release of noradrenaline in the brain, by activation of locus cerulean neurons. The release of corticotrophin releasing factor as neurotransmitter in the locus coeruleus leads to the activation of medullary centers, which control the sympathetic nervous system. Sympathetic processes may stimulate a neural pathway via ganglia, and an endocrine pathway that elicits the release of catecholamines, epinephrine and norepinephrine, into the circulation by the adrenal glands. Circulating catecholamines stimulate effector organs via specific adrenergic receptors [4]. Nevertheless, it has nowadays become evident that the dopamine system plays a key role in the response to stress, most especially in the pathological response observed in many psychiatric disorders.

Dopaminergic system and stress

The catecholamine dopamine serves as a neurotransmitter in several important pathways in the CNS where it controls a variety of functions including locomotor activity, cognition, emotion, positive reinforcement, food intake, and endocrine regulation [5]. Neurons in the adult bilateral mesodiencephalic dopamine system (A8–A10) give rise to prominent forebrain projections and receive inputs from various other brain regions. Dopamine containing neurons can be divided into four main groups: nigrostriatal, mesolimbic, mesocortical and tuberohypophysial [6].

Dopamine is synthesized from the essential aminoacid tyrosine by the rate-limiting enzyme, tyrosine hydroxylase (TH), to form L-3, 4-dihydroxyphenylalanine (L-DOPA). L-DOPA is thereafter decarboxylated by aromatic L-amino acid decarboxylase to form dopamine [7]. All known physiological functions of dopamine are mediated by five subtypes termed D1 to D5 dopaminergic receptors. All are G-protein-coupled receptors (GPCRs) with seven hydrophobic domains, an extracellular N-terminus and an intracellular C terminus segment. Based on their property to couple to either Gαs proteins or Gαi proteins that stimulate or inhibit the production of the second messenger cAMP, respectively, dopamine receptors are classified as D1-class receptors (D1 and D5) or D2-class receptors (D2, D3 and D4) [8,9]. The D1 receptor is the most widespread dopamine receptor and is found in the nucleus accumbens, amygdala, caudate putamen and prefrontal cortex. D5 is mostly expressed in the frontal cortex, hippocampus and caudate putamen. The three D2 type receptors D2, D3 and D4 are primarily expressed in the nucleus accumbens, and olfactory tubercle. In addition, D2 is also expressed in caudate putamen, D3 in Island of Calleja and ventrotegmental area, and D4 in hippocampus, caudate putamen and frontal cortex [5,10].

Several studies in the past decades, have convincingly demonstrated that DA plays a key role in the response to stress, and that the DA system is activated by maintained stressful stimuli [11]. Out of the four main pathways described, the mesolimbic system seems to be mainly implicated in this response since it is involved in the processing of natural and artificial rewards mediating the hedonic aspects of rewarding stimuli [12], acting as a learning signal for behavioural reinforcement [13], and involved in motivation and attention processes [14,15].

It is well known that chronic stress yields devastating effects including cognitive and working memory dysfunctions, for which transmission mediated by catecholamines

dopamine and noradrenaline in the prefrontal cortex is crucial. Since catecholamine synthesis depends on the rate-limiting enzyme TH, this enzyme is thought to play an important role in prefrontal cortex function. There is an association between tyrosine hydroxylase expression in the prefrontal cortex and working memory, which produces two distinct population of rats in terms of working memory capacity and response to chronic stress [16].

Acute footshock stress leads to activation of TH in the locus coeruleus, pre-synaptic terminals in the mPFC and adrenal medullary chromaffin cells, as well as changes inactivity of the HPA axis [17]. On the other hand, acute immobilization prevents locus coeruleus TH mRNA levels from rising significantly, while glucocorticoids appear to decrease their capacity to restrain locus coeruleus TH mRNA during repeated immobilization [18].

There seems to be links between catecholamines (norepinephrine and dopamine) with corticotrophin-releasing factor and drug addiction. To illustrate, compulsive drug use associated with dependence is mediated by loss of function of reward systems and recruitment of key brain stress systems such as corticotrophin-releasing factor and norepinephrine in the extended amygdala. It has been advanced that addiction processes involve a profound activation of stress systems in the brain that interact but are independent of hormonal stress systems [19]. The ability of drug of abuse to enhance extracellular concentrations of dopamine in the nucleus accumbens seems to be a crucial common denominator for the development of drug addiction [20] and corticotrophin-releasing factor participates in stress-induced drug abuse [21].

Early life stress has also been largely studied in relation to the dopaminergic neurotransmission. Restraint stress exerted onto the pregnant dam produces long lasting effects on the dopaminergic development of the offspring. Accordingly, prenatal stress increases dopamine D2 receptors in limbic areas, decreases dopamine stimulated release in cortical areas whereas it increases in NAc, disrupts the dopamine-glutamate balance and impairs the expression of specific TFs along development as well as the expression of TH and transporters [22].

Neurotensinergic system and stress

Neurotensin is a tridecapeptide widely distributed in the nervous system, at both central and peripheral levels. It can behave as a neurotransmitter or as a

neuromodulator, exerting diverse biological actions [23]. Neurotensin is involved in various processes, such as reward, locomotion, pain modulation and stress. Administration of neurotensin to the central nervous system produces a wide variety of effects, including the regulation of the stress response [24,25].

Neurotensin actions are mediated by its binding to a group of receptors [26]. Two of them, denominated NTS1 and NTS2 receptors, bind neurotensin with high and low affinity, respectively. Both belong to the seven transmembrane domain receptors family coupled to G proteins. Another two neurotensin receptor types are mainly localized intracellularly and are termed NTS3/sortilin and nts4/SorLA [27]. The diverse functions of neurotensin at central nervous system have been reviewed [28].

Radioimmunoassays carried out in brain of a variety of species disclosed neurotensin distribution. High levels of this peptide are found in hypothalamus and basal forebrain, intermediate concentrations are found in basal ganglia, brainstem and dorsal horn of the spinal cord whereas low levels are found in thalamus and cortex (see [25,29]). Most interesting, neurotensin and NTS1 receptor are densely localized in areas that process emotion (amygdala nucleus), the response to stress (hypothalamic nucleus) and/or cognition (such as hippocampal nuclei and cortical areas) (see [30]).

Glucocorticoids and their receptors are present in most neuronal cells, in accordance with their widespread actions on neuronal metabolism and are known to be key elements in the stress situation. Steroid hormones released from peripheral endocrine glands may directly regulate brain functions through specific brain areas. These effects may be rapid or alternatively, involve long-term changes at the genomic level (for references, see [31]). High densities of neurotensin terminals and neurotensin binding are present in the parvocellular division of the paraventricular nucleus where corticotrophin-releasing factor-producing neurons are present [32,33].

Intracerebroventricular administration of neurotensin enhances plasma levels of adrenocorticotropic hormone from anterior pituitary and corticosterone from adrenal gland [33,34]. It has been suggested that endogenous neurotensin regulates HPA axis activity in stress condition by increasing corticosterone plasma levels [33,35-38]. Data from recent years have accumulated suggesting that neurotensin is physiologically involved in the regulation of the HPA axis, modulating ACTH and corticosterone release. Several studies including administration of neurotensin, lesion of the hypothalamus and antagonist administration among others, illustrate this observation: a) Central administration of neurotensin activates the HPA axis, an effect most likely

dependent upon the release of corticotrophin-releasing factor. Film and emulsion autoradiography shows that ^{125}I-neurotensin labels hypothalamic nucleus, with relatively high densities of neurotensin binding sites in the paraventricular nucleus. SR 48692 and its analogue 48450, antagonists for NTS1 receptor, compete for ^{125}I-neurotensin binding. These findings indicate that the hypothalamus and the HPA axis may be the anatomical substrate for neurotensin effects on neuroendocrine functions (for references, see [33]). b) Bilateral lesions of the paraventricular nucleus of the hypothalamus markedly reduces neurotensin stimulation of ACTH and corticosterone release, indicating that the paraventricular nucleus is essential for neurotensin stimulatory action [35]. During heat stress significant elevations in blood level of corticosterone and ACTH, indicators of the HPA axis, are recorded. At the same time, neurotensin increases in the hypothalamus but diminishes in the nucleus accumbens [39]. c) HPA function was studied under basal conditions and during restraint stress after central administration of NTS1 receptor antagonist SR 48692. Chronic administration of this antagonist to the paraventricular nucleus of the hypothalamus attenuates both diurnal and stress-induced enhancements in HPA activity. SR 48692 diminishes the diurnal enhancement in plasma ACTH and corticosterone during the evening phase of the cycle whereas it fails to modify morning levels. Restraint-induced enhancement in plasma ACTH and corticosterone levels are also reduced in SR 48692 treated animals. Results suggested that SR 48692 effects are restricted to periods of stimulated HPA activity. A decrease in corticotrophin-releasing hormone-like immunoreactivity is observed in the paraventricular nucleus following chronic SR 48692. Besides, a parallel decrease in corticotrophin-releasing hormone-like immunoreactivity is recorded in the external area of the median eminence. Findings suggest that endogenous neurotensin leads to the increase in HPA activity during periods of enhanced stimulation (for references, see [36]). d) The secretion of ACTH depends on hypophysiotrophic factors released from neurons of paraventricular nucleus of the hypothalamus**.** Potential role of neurotensin in the regulation of the different components of the HPA axis under basal and stress conditions have been investigated. Implants of SR 48692 above the paraventricular nucleus reduce ACTH and corticosterone plasma levels after tail cut procedure. Besides, exposure of animals to a novel environment for 30 min reduces ACTH and corticosterone plasma levels in the SR 48692 treated group. Chronic administration of SR 48692 reduces corticotrophin-releasing factor mRNA in the parvocellular division of the paraventricular nucleus of

the hypothalamus. This treatment likewise enhances vasopressin and vasopressin mRNA levels in the magnocellular neurons of the paraventricular nucleus whereas oxytocin plasma levels are not affected. Findings suggest that endogenous neurotensin in the paraventricular nucleus plays a tonic stimulatory role on HPA axis but an inhibitory effect on vasopressin secretion (for references, see [35]).

It is known that stress activates neural systems that suppress pain sensation, denominated stress-induced analgesia [40], in which neurotensin plays an important role [27]. In fact, exogenous neurotensin produces pain inhibition regardless of the way of administration or the analgesic test employed [41]. Stress-induced analgesia following water avoidance or restraint stress is reduced in neurotensin-deficient mice. Moreover, genetic and pharmacological approaches show that NTS2 receptors mediate this non-opiod stress-induced analgesia. Accordingly, mice lacking NTS2 receptor exhibit reduced stress-induced analgesia following cold water swim stress [38].

Reports on the effect of stress on the NT system, mostly depends on the type of stress as much as the brain area studied. To offer some few examples, cold swim stress exerts an increase of the NT mRNA in the lateral hypothalamus and the medial preoptic area [42]. Cold water restraint decreases NT mRNA and levels of NT in Nucleus accumbens, increases NTR binding sites and decreases NTR mRNA. [43], Whole-body vibration stress exerts an increase of NT-like immunoreactivity in frontal cortex and hypothalamus [44]. Evidence indicates that stress during postnatal development is associated with enhanced risk for anxiety disorders, depression as well as substance abuse later in life. Maternal separation enhances freezing behaviours in fear-conditioned stress and decreases the gene expression of NTS1 receptor but not that of neurotensin or NTS2 receptor in amygdala of adult rats (for references, see [30]).

Taken together these studies clearly demonstrate not only that the infliction of a stress insult alters the neurotensinergic system but that neurotensin exerts a physiological modulation of the HPA axis.

Interactions between dopaminergic and neurotensinergic systems

There is nowadays little doubt on the existing interaction between dopaminergic and neurotensinergic systems both from an anatomical and a biochemical point of view [45,46]. To illustrate the anatomical distribution, main areas and pathways for both systems are shown in Figure 1. For a detailed background on the experimental evidence supporting this interaction the reader is referred to excellent reviews on this subject

[25,47]. In brief, there are anatomical and functional interactions between neurotensin, the mesotelencephalic dopamine system and structures innervated by dopaminergic projections [46]. Experimental results come from several approaches, including the study of neurotensin effects on the mesotelencephalic dopaminergic projections, the action of dopamine on neurotensin levels in some brain areas (striatum, ventral mesencephalon and limbic forebrain), the detection of neurotensin (immunohistochemically) or that of neurotensin/neuromedin mRNA after dopamine receptor blockade and stimulation at striatum (for original articles, see [25]).

Moreover, evidence obtained from biochemical binding, microdialysis, electrophysiological and co-immunoprecipitation studies, as well as from biophysical approaches, specially bioluminescence resonance energy transfer (BRET2) (see [47,48] for references) has convincingly demonstrated the existence of an heteromer composed by the NTS1 receptor and dopaminergic D2 receptor. Both receptors are GPCRs but dopaminergic D2 receptor family exhibits a wide variety of signaling diversity which is due to numerous factors, including the ability of receptors to adopt multiple active states with particular effector-coupling profiles. Among this is the ability to form homo- or heterodimers with proper signaling, pharmacology as well as receptor activation from desensitization and internalization [49]. Allosteric mechanisms between these receptors may be operative and selective antagonistic NTS1 receptor-D2 receptor interactions enhance the diversity of dopamine signaling by decreasing dopaminergic D2 receptor-mediated dopamine signaling over dopaminergic D1 receptor-mediated dopamine signaling [50].

It is important to point out that the effects of neurotensin on the dopamine system has the obvious potential implication in many diseases of the CNS traditionally linked to dopamine such as stress, schizophrenia, psychostimulant drug abuse and Parkinson among others [25,47,51]. It is of interest to remark that among all these pathologies, particular attention should be considered in relation to drug abuse and stress, as already pointed out [25].

Concomitant alteration of dopaminergic and neurotensinergic systems under stress condition

As mentioned above many pathological conditions has been linked to stress and a wealth of studies suggest a link between central DA systems and the HPA axis. Since

neurotensin system spreads consistently in the DAergic and HPA axis, it has been suggested that neurotensin play a critical role in mediating the linkage.

The exposure to acute mild footshock produces a selective and regionally specific enhancement in neurotensin-like immunoreactivity concentrations in the ventral tegmental area. It should be recalled that this area is the source of the dopaminergic innervation of the mesocortical and mesolimbic dopaminergic regions. Interestingly, levels of dopamine metabolite, 3, 4-dihydroxyphenylacetic acid, increase only in the ventral tegmental area and medial prefrontal cortex. These findings led to the suggestion that neurotensin in the ventral tegmental area is involved in activation of certain mesotelencephalic dopamine neurons [52].

The central amygdaloid nucleus is part of the amygdaloid body, known to participate in several stress related situations. Immunocytochemical studies disclosed that this area is densely innervated by nerve terminals containing factors potentially involved in stress. Some of them are TH, corticotrophin releasing factor and neurotensin. Immunoreactivity for corticotrophin releasing factor and neurotensin are present in perikarya of numerous neurons in this area (for references, see [53]). Stress stimulates the expression of the immediate early gene c-fos in parvocellular neurons of the paraventricular nucleus, many of its neurons also contain corticotrophin-releasing factor immunoreactivity [54]. Besides, after stress immobilization, colocalization of Fos and glucocorticoid receptor-like immunoreactivities was shown in the amygdaloid complex [50]. Immunocytochemical double staining disclosed colocalization of the Fos-immunoreactive neurons with peptide and TH containing structures. Immobilization stress enhances Fos, peptide and TH immunoreactive neurons. These results suggest that stress increases the synaptic activity of the central amygdaloid nucleus, which stimulates c-fos expression. In turn, Fos may regulate the expression of several peptide genes, including those for neurotensin and corticotrophin releasing factor, thus affecting the peptidergic efferent from the central amygdaloid nucleus (for references, see [53]).

Catecholamines and neurotensin in the central amygdaloid nucleus have been implicated in the integration of the autonomic response to stress. The cellular substrate for this integration was investigated with rat antiserum against neurotensin and rabbit antiserum against catecholamine-synthesizing enzyme, TH. These studies led to the ultrastructural localization and dual localization in the central amygdaloid nucleus by peroxidase-antiperoxidase and immunoautoradiography methods. In single and dual labeling assays, neurotensin-like immunoreactivity is detected in perikarya and

processes. In the dual labeling assay, perikarya contain only neurotensin-like immunoreactivity while nerve endings contain TH and/or neurotensin-like immunoreactivity. Findings indicate that in rat central amygdaloid nucleus two populations of neurons differ regarding to the distribution of neurotensin, and that the output from neurons containing neurotensin is modulated by direct input from nerve endings containing neurotensin and/or catecholamines [55]. The release of neurotensin and catecholamines (most likely dopamine), from the same or from distinct nerve terminals on common targets in the central amygdaloid nucleus may explain certain similarities in the functions of these neuroactive substances related to stress [55].

There is evidence indicating that neurotensin modulates selectively the dopamine mesolimbic system when compared with the mesocortical pathway. Daily i.p. administration of SR 48692 to rats for 15 days leads to the increase in the expression of tyrosine hydroxylase mRNA and protein in the ventral mesencephalon. Simultaneous *in vivo* microdialysis in the nucleus accumbens shell and the medial prefrontal cortex discloses that neurotensin receptor blockade for 15 days decreases basal dopamine extracellular levels and its metabolites in the nucleus accumbens shell whereas dopamine levels in the medial prefrontal cortex remain unchanged. In animals subjected to a forced swimming stress, which enhances extracellular dopamine levels in the medial prefrontal cortex, administration of SR 48692 fails to modify the stress-induced enhancement in dopamine.

Another interesting result is related to the modulation of mesencephalic dopamine neurons by glucocorticoids. The repeated treatment with the neurotensin receptor antagonist fails to modify basal levels of free corticosterone but reduces the increase induced by forced swimming stress [37]. These findings suggest the involvement of NTS1 receptor in the modulation of mesencephalic dopamine neurons in the stress behaviour.

The human neuroblastoma cell line CHP212 expresses functional high affinity NTS1. The exposure of these cells to JMV 449, a stable neurotensin agonist, increases TH protein and mRNA. JMV 449 effect occurs by an increase in the transcriptional activity of the TH gene. These findings indicate that modulation of TH gene expression may be one of the mechanisms involved in dopamine transmission control by neurotensin. It has been suggested that the observed changes may likewise participate in adaptation processes at central nervous system where neurotensin is released, such as food intake and stress condition [56].

To sum up, the key lines of evidence for the co-ordinate functions of the dopamine and neurotensin systems under stress condition arise from immunocytochemical studies. Within this context, the areas more critically involved are the ventral tegmental area, the central amygdaloid nucleus, the mesotelencephalus and the medial prefrontal cortex.

These examples clearly illustrate the close interrelation between the neurotensinergic and the dopaminergic systems and, in turn, both with the HPA axis. Corticosteroids released during stress are able to activate the reward systems inducing an increase of DA release, especially in the nucleus accumbens. The effect of neurotensin on ventral mesencephalic DA, oppose the action of DA, which, via DA autoreceptors, decreases DA neuron activity and reduces DA release in the NAc. Therefore NT is regarded as a modulator of mesotelencephalic DA that might have a crucial role in stress behaviours.

Concluding remarks

In the present article available experimental evidence was reviewed, which shows close interaction between dopamine D2 and neurotensin NTS1 receptors, supporting a functional link between these macromolecules under stress condition.

There is the notion that stress occurs in response to factors (stressors) being threatening, aversive or excessive to maintain the physiological equilibrium of an organism. It is observed that reiterate exposure to stressors, especially during early life, is often related to later psychiatric disorders. One of the potential candidate mechanisms is the HPA axis, with excessive release of cortisol from adrenal cortex. This process is closely related to several neuroactive substances, including amino acid neurotransmitters, catecholamines, and serotonin as well as neuroactive peptides.

Stress conditions are likewise related to neurogenesis and neuroplasticity and generation of free radicals which lead to oxidative stress. It should be taken into consideration the activation of the limbic-HPAaxis and the release of glucocorticoids is fundamental for the adaptive response and immediate survival of an organism in response to acute stimuli. However, high levels of glucocorticoids in brain may lead to neuronal injury and affecting neurotransmitter signaling, neural activity and animal behavior.

Evidence indicates that disregulation of the brain emotional systems that mediate stress and arousal is a key component of the pathophysiology of drug addiction.

Therefore, information provided in the present article may be of interest to unveal molecular mechanisms involved in drug addiction. It would be of interest to investigate whether a correlation exists between drug withdrawal and reward through corticotrophin-releasing factor, dopamine release in nucleus accumbens and neurotensinergic system.

It is desirable that basic research throw light about the molecular mechanisms involved in catecholamine and neurotensin neurotransmission as well as on the cross-talk between dopaminergic D2 receptor and neurotensinergic NTS1 receptor. Another line of research might be focused on signaling resulting of dopamine D2 and NTS1 receptors activation as a cause of stress. These notions will allow introducing specific and selective pharmacological approaches leading to tools which may be preventive or therapeutic for psychiatric illnesses produced by stress conditions (see [57]).

It is expected that the focus in the present review, namely neurotensin and dopamine may allow to draw attention on relevant relations among these neurotransmitters to disclose the mechanisms that control stress behaviour.

Acknowledgments: The authors are Senior Researchers from the Consejo Nacional de Investigaciones Científicas y Técnicas, Argentina (CONICET). Financial support from CONICET (PIP 0249 to MCA) is acknowledged.

Conflict of interest: The authors declare that they have no conflict of interest.

References

1. Lucassen P, Pruessner J, Sousa N, Almeida OX, Van Dam A, Rajkowska G, Swaab D, Czéh B (2014) Neuropathology of stress. Acta Neuropathologica 127 (1):109-135. doi:10.1007/s00401-013-1223-5

2. Koolhaas J, Bartolomucci A, Buwalda B, de Boer S, Flügge G, Korte S, Meerlo P, Murison R, Olivier B, Palanza P, Richter-Levin G, Sgoifo A, Steimer T, Stiedl O, van Dijk G, Wöhr M, Fuchs E (2011) Stress revisited: A critical evaluation of the stress concept. Neuroscience & Biobehavioral Reviews 35 (5):1291-1301. doi:http://dx.doi.org/10.1016/j.neubiorev.2011.02.003

3. Chrousos G (2009) Stress and disorders of the stress system. Nat Rev Endocrinol 5 (7):374-381. doi:nrendo.2009.106 [pii]10.1038/nrendo.2009.106

4. Schulz A, Vögele C (2015) Interoception and stress. Frontiers in Psychology 6:993. doi:10.3389/fpsyg.2015.00993

5. Missale C, Nash SR, Robinson SW, Jaber M, Caron MG (1998) Dopamine receptors: from structure to function. Physiol Rev 78 (1):189-225

6. Gnegy M (2012) Catecholamines. In: Price STBJSWAL (ed) Basic Neurochemistry (Eighth Edition). Academic Press, New York, pp 283-299. doi:http://dx.doi.org/10.1016/B978-0-12-374947-5.00014-6

7. Shiman R, Akino M, Kaufman S (1971) Solubilization and partial purification of tyrosine hydroxylase from bovine adrenal medulla. J Biol Chem 246 (5):1330-1340

8. Kebabian J (1978) Multiple classes of dopamine receptors in mammalian central nervous system: the involvement of dopamine-sensitive adenylyl cyclase. Life Science 23 (5):479-483

9. Spano P, Govoni S, Trabucchi M (1978) Studies on the pharmacological properties of dopamine receptors in various areas of the central nervous system. Advances in Biochemical Psychopharmacology 19:155-165

10. Xu M, Zhang J (2004) Molecular genetic probing of dopamine receptors in drug addiction. Curr Opin Drug Discov Devel 7 (5):703-708

11. Piazza P, Le Moal M (1998) The role of stress in drug self-administration. Trends in Pharmacological Sciences 19 (2):67-74. doi:http://dx.doi.org/10.1016/S0165-6147(97)01115-2

12. Wise R, Rompre P (1989) Brain Dopamine and Reward. Annual Review of Psychology 40 (1):191-225. doi:doi:10.1146/annurev.ps.40.020189.001203

13. Schultz W (1997) Dopamine neurons and their role in reward mechanisms. Current Opinion in Neurobiology 7 (2):191-197. doi:S0959-4388(97)80007-4 [pii]

14. Berridge K, Robinson T (1998) What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Research Reviews 28 (3):309-369. doi:http://dx.doi.org/10.1016/S0165-0173(98)00019-8

15. Salamone JD, Cousins M, Snyder B (1997) Behavioral functions of nucleus accumbens dopamine: Empirical and conceptual problems with the anhedonia hypothesis. Neuroscience & Biobehavioral Reviews 21 (3):341-359. doi:http://dx.doi.org/10.1016/S0149-7634(96)00017-6

16. Lee Y-A, Goto Y (2015) Chronic stress effects on working memory: Association with prefrontal cortical tyrosine hydroxylase. Behavioural Brain Research 286:122-127. doi:http://dx.doi.org/10.1016/j.bbr.2015.03.007

17. Ong LK, Guan L, Damanhuri H, Goodchild AK, Bobrovskaya L, Dickson PW, Dunkley PR (2014) Neurobiological consequences of acute footshock stress: effects on tyrosine hydroxylase phosphorylation and activation in the rat brain and adrenal medulla. Journal of Neurochemistry 128 (4):547-560. doi:10.1111/jnc.12482

18. Makino S, Smith MA, Gold PW (2002) Regulatory role of glucocorticoids and glucocorticoid receptor mRNA levels on tyrosine hydroxylase gene expression in the locus coeruleus during repeated immobilization stress. Brain Research 943 (2):216-223. doi:http://dx.doi.org/10.1016/S0006-8993(02)02647-1

19. Koob G (2009) Brain stress systems in the amygdala and addiction. Brain Research 1293:61-75. doi:10.1016/j.brainres.2009.03.038
20. Willuhn I, Wanat M, Clark J, PE P (2009) Dopamine Signaling in the Nucleus Accumbens of Animals Self-Administered Drugs of Abuse. In: Behavioral Neuroscience of Drug Addiction, Current Topics in Behavioral Neurosciences, vol 3. pp 29-71
21. Haass-Koffler C, Bartlett S (2012) Stress and addiction: contribution of the corticotropin releasing factor (CRF) system in neuroplasticity. Frontiers in Molecular Neuroscience 5:91. doi:10.3389/fnmol.2012.00091
22. Baier C, Katunar M, Adrover E, Pallarés M, Antonelli M (2012) Gestational Restraint Stress and the Developing Dopaminergic System: An Overview. Neurotox Res 22 (1):16-32. doi:10.1007/s12640-011-9305-4
23. Kitabgi P, Nemeroff C (1992) The Neurobiology of Neurotensin. Annals of the New York Academy of Sciences 668
24. Kinkead B, Nemeroff C (2004) Neurotensin, Schizophrenia, and Antipsychotic Drug Action. In: International Review of Neurobiology, vol Volume 59. Academic Press, pp 327-349. doi:http://dx.doi.org/10.1016/S0074-7742(04)59013-X
25. Geisler S, Bérod A, Zahm D, Rostène W (2006) Brain neurotensin, psychostimulants, and stress – emphasis on neuroanatomical substrates. Peptides 27 (10):2364-2384. doi:http://dx.doi.org/10.1016/j.peptides.2006.03.037
26. Vincent J-P, Mazella J, Kitabgi P (1999) Neurotensin and neurotensin receptors. Trends in Pharmacological Sciences 20 (7):302-309. doi:http://dx.doi.org/10.1016/S0165-6147(99)01357-7
27. Dobner P (2005) Multitasking with neurotensin in the central nervous system. Cell Mol Life Sci 62 (17):1946-1963. doi:10.1007/s00018-005-5128-x
28. López Ordieres M, Rodríguez de Lores Arnaiz G (2009) Neurotensin in central neurotransmission. In: Rodríguez de Lores Arnaiz G (ed) Function of Neuropeptides at Central Nervous System Research Signpost, Trivandrum, Kerala, India, pp 1-30
29. Emson P, Goedert M, Horsfield P, Rioux F, St. Pierre S (1982) The Regional Distribution and Chromatographic Characterisation of Neurotensin-Like Immunoreactivity in the Rat Central Nervous System. Journal of Neurochemistry 38 (4):992-999. doi:10.1111/j.1471-4159.1982.tb05340.x
30. Toda H, Boku S, Nakagawa S, Inoue T, Kato A, Takamura N, Song N, Nibuya M, Koyama T, Kusumi I (2014) Maternal Separation Enhances Conditioned Fear and Decreases the mRNA Levels of the Neurotensin Receptor 1 Gene with Hypermethylation of This Gene in the Rat Amygdala. PLoS ONE 9 (5):e97421. doi:10.1371/journal.pone.0097421
31. Rostène W, Sarrieau A, Nicot A, Scarceriaux V, Betancur C, Gully D, Meaney M, Rowe W, De Kloet R, Pelaprat D (1995) Steroid effects on brain functions: an example of the action of glucocorticoids on central dopaminergic and neurotensinergic systems. Journal of Psychiatry and Neuroscience 20 (5):349-356
32. Sawchenko P, Swanson L, Vale W (1984) Corticotropin-releasing factor: co-expression within distinct subsets of oxytocin-, vasopressin-, and neurotensin-immunoreactive neurons in the hypothalamus of the male rat. The Journal of Neuroscience 4 (4):1118-1129
33. Nicot A, Bérod A, Gully D, Rowe W, Quirion R, de Kloet E, Rostène W (1994) Blockade of neurotensin binding in the rat hypothalamus and of the central action of neurotensin on the hypothalamic-pituitary-adrenal axis with non-peptide receptor antagonists. Neuroendocrinology 59 (6):572-578
34. Gudelsky G, Berry S, Meltzer H (1989) Neurotensin Activates Tuberoinfundibular Dopamine Neurons and Increases Serum Corticosterone Concentrations in the Rat. Neuroendocrinology 49 (6):604-609
35. Nicot A, Rowe W, De Kloet E, Betancur C, Jessop D, Lightman S, Quirion R, Rostène W, Bérod A (1997) Endogenous Neurotensin Regulates Hypothalamic-Pituitary-Adrenal Axis

Activity and Peptidergic Neurons in the Rat Hypothalamic Paraventricular Nucleus. Journal of Neuroendocrinology 9 (4):263-269. doi:10.1046/j.1365-2826.1997.00581.x
36. Rowe W, Nicot A, Sharma S, Gully D, Walker C, Rostène W, Meaney M, Quirion R (1997) Central Administration of the Neurotensin Receptor Antagonist, SR48692, Modulates Diurnal and Stress-Related Hypothalamic-Pituitary-Adrenal Activity. Neuroendocrinology 66 (2):75-85
37. Azzi M, Betancur C, Sillaber I, Spanagel R, Rostène W, Bérod A (1998) Repeated Administration of the Neurotensin Receptor Antagonist SR 48692 Differentially Regulates Mesocortical and Mesolimbic Dopaminergic Systems. Journal of Neurochemistry 71 (3):1158-1167. doi:10.1046/j.1471-4159.1998.71031158.x
38. Gui X, Carraway R, Dobner P (2004) Endogenous neurotensin facilitates visceral nociception and is required for stress-induced antinociception in mice and rats. Neuroscience 126 (4):1023-1032. doi:http://dx.doi.org/10.1016/j.neuroscience.2004.04.034
39. Nakamura H, Seto T, Nagase H, Yoshida M, Hatta K, Matsuzaki I, Ogino K (1997) Involvement of Central Neurotensin in Thermoregulatory and Neuroimmune Function in Pregnant Rats Exposed to Heat. Brain, Behavior, and Immunity 11 (2):141-152. doi:http://dx.doi.org/10.1006/brbi.1997.0487
40. Amit Z, Galina Z (1986) Stress-induced analgesia: adaptive pain suppression. Physiological Reviews 66 (4):1091-1120
41. Dobner P (2006) Neurotensin and pain modulation. Peptides 27 (10):2405-2414. doi:http://dx.doi.org/10.1016/j.peptides.2006.04.025
42. Seta K, Jansen H, Kreitel K, Lehman M, Behbehani M (2001) Cold water swim stress increases the expression of neurotensin mRNA in the lateral hypothalamus and medial preoptic regions of the rat brain. Molecular Brain Research 86 (1–2):145-152. doi:http://dx.doi.org/10.1016/S0169-328X(00)00279-5
43. Xing L, Karinch A, Kauffman GL (1998) Mesolimbic expression of neurotensin and neurotensin receptor during stress-induced gastric mucosal injury. American Journal of Physiology - Regulatory, Integrative and Comparative Physiology 274 (1):R38-R45
44. Nakamura H, Moroji T, Nohara S, Nakamura H, Okada A (1990) Effects of whole-body vibration stress on substance P- and neurotensin-like immunoreactivity in the rat brain. Environmental Research 52:155-163
45. Nemeroff C, Cain S (1985) Neurotensin-dopamine interactions in the CNS. Trends Pharmacological Sciences 6:201-205
46. Binder E, Kinkead B, Owens M, Nemeroff C (2001) Neurotensin and dopamine interactions. Pharmacol Reviews 53 (4):453-486
47. Ferraro L, Beggiato S, Borroto-Escuela D, Ravani L, O'Connor W, Tomasini M, Borelli A, Agnati L, Antonelli T, Tanganelli S, Fuxe K (2014) Neurotensin NTS1-dopamine D2 receptor-receptor interactions in putative receptor heteromers: relevance for Parkinson`s disease and schizophrenia. Current Protein & Peptide Science 15:681-690
48. Bai M (2004) Dimerization of G-protein-coupled receptors: roles in signal transduction. Cellular Signalling 16 (2):175-186. doi:http://dx.doi.org/10.1016/S0898-6568(03)00128-1
49. Maudsley S, Martin B, Luttrell L (2005) The Origins of Diversity and Specificity in G Protein-Coupled Receptor Signaling. The Journal of pharmacology and experimental therapeutics 314 (2):485-494. doi:10.1124/jpet.105.083121
50. Fuxe K, Tarakanov A, Romero Fernandez W, Ferraro L, Tanganelli S, Filip M, Agnati L, Garriga P, Diaz-Cabiale Z, Borroto-Escuela D (2014) Diversity and Bias through Receptor–Receptor Interactions in GPCR Heteroreceptor Complexes. Focus on Examples from Dopamine D2 Receptor Heteromerization. Frontiers in Endocrinology 5:71. doi:10.3389/fendo.2014.00071
51. St-Gelais F, Jomphe C, Trudeau L-É (2006) The role of neurotensin in central nervous system pathophysiology: What is the evidence? Journal of Psychiatry and Neuroscience 31 (4):229-245

52. Deutch A, Bean A, Bissette G, Nemeroff C, Robbins R, Roth R (1987) Stress-induced alterations in neurotensin, somatostatin and corticotropin-releasing factor in mesotelencephalic dopamine system regions. Brain Research 417 (2):350-354. doi:http://dx.doi.org/10.1016/0006-8993(87)90462-8
53. Honkaniemi J (1992) Colocalization of peptide- and tyrosine hydroxylase-like immunoreactivities with Fos-immunoreactive neurons in rat central amygdaloid nucleus after immobilization stress. Brain Research 598 (1–2):107-113. doi:http://dx.doi.org/10.1016/0006-8993(92)90173-7
54. Ceccatelli S, Villar M, Goldstein M, Hökfelt T (1989) Expression of c-Fos immunoreactivity in transmitter-characterized neurons after stress. Proceedings of the National Academy of Sciences of the United States of America 86 (23):9569-9573
55. Bayer V, Towle A, Pickel V (1991) Vesicular and cytoplasmic localization of neurotensin-like immunoreactivity (NTLI) in neurons postsynaptic to terminals containing NTLI and/or tyrosine hydroxylase in the rat central nucleus of the amygdala. Journal of neuroscience research 30 (2):398-413.
56. Najimi M, Hermans E, Rostène W, Forgez P (2001) Transcriptional Regulation of the Tyrosine Hydroxylase Gene by Neurotensin in Human Neuroblastoma CHP212 Cells. Metabolic Brain Disease 16 (3):165-174. doi:10.1023/a:1012588927052
57. Ventriglio A, Gentile A, Baldessarini R, Bellomo A (2015) Early-Life Stress and Psychiatric Disorders: Epidemiology, Neurobiology and Innovative Pharmacological Targets. Current Pharmaceutical Design 21:1379-1387. doi:10.2174/1381612821666150105121244

FIGURE LEGENDS

Figure 1:

Schematic representation of the main A) dopaminergic and B) neurotensinergic pathways in the rat brain. It should be noted that both neurotransmitters are localized in areas that are related to the response to stress (such as hypothalamic nucleus), as well as in areas that process emotion (such as amygdala nuclei) and/or cognition (such as hippocampal nuclei and cortical areas). DFC: Dorsal Frontal Cortex. PFC: Prefrontal Cortex. Hip: Hippocampus. Cpu: Caudate Putamen. Nac: Nucleus Accumbens. SN: Sustantia Nigra. VTA: Ventral Tegmental Area. ENT Cx: Entorhinal Cortex. LS: Lateral Septum.PIR: Piriform area. Amy: Amygdala.

Figure

Click here to download Figure Figura 1.tif