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Animal models of social stress: Effects on behavior and brain neurochemical systems

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Abstract

Social interactions serve as an evolutionarily important source of stress, and one that is virtually ubiquitous among mammalian species. Animal models of social stress are varied, ranging from a focus on acute, intermittent, or chronic exposure involving agonistic behavior, to social isolation. The relative stressfulness of these experiences may depend on the species, sex, and age of the subjects, and subject sex also appears to influence the value of hypothalamic–pituitary–adrenal (HPA) axis activity as a general criterion for stress response: higher glucocorticoid levels are typically found in dominant females in some species. Social stress models often produce victorious and defeated, or dominant and subordinate, animals that may be compared to each other or to controls, but the appropriateness of specific types of comparisons and the interpretations of their differences may vary for the different models. Social stress strongly impacts behavior, generally reducing aggression and enhancing defensiveness, both inside and outside the stress situation. Social and sexual behaviors may be reduced in subordinate animals, as is activity and responsivity to normally rewarding events. However, some components of these changes may be dependent on the presence of a dominant, rather than representing a longer-term and general alteration in behavior. Social stress effects on brain neurotransmitter systems have been most extensively investigated, and most often found in serotonin and noradrenergic systems, with changes also reported for other monoamine and for peptidergic systems. Morphological changes and alterations of neogenesis and of cell survival particularly involving the hippocampus and dentate gyrus have been reported with severe social stress, as have longer-term changes in HPA axis functioning. These findings indicate that social stress models can provide high magnitude and appropriate stressors for research, but additionally suggest a need for caution in interpretation of the findings of these models and care in analysis of their underlying mechanisms.

Keywords: Social stress; Subordination; Social defeat; Social disruption; Social instability; Social isolation; Rats; Mice; Tree shrews; Hypothalamic–pituitary–adrenal axis

1. Social interactions as prototypical stressors

Recent work suggests that different types of stressful events may sometimes produce qualitatively different patterns of effects in both behavior and physiology. Repeated social defeat and electric foot shock produce opposite effects on systolic blood pressure and mean arterial blood pressure, with enhancement in the former situation and decrement in the latter [1]. While fear of foot shock produced both bradycardia and immobility in almost all rat subjects, fear of a dominant rat produced different effects in different subsets of subjects, with about 50% showing bradycardia, and the others primarily expressing immobility [100] Although water deprivation produced a duration-dependent anxiolytic effect in the elevated plus maze, 1-h restraint was anxiogenic in the same situation [76]. Social defeat decreased the variability of a number of indexes of cardiac electrical activity parameters, while three nonsocial stressors (restraint, shock-probe test, and swimming) either increased or failed to change this variability [104]. Social, but not restraint, stress reactivated a latent HSV type 1A virus [95]. A variety of stressors tend to elicit self-grooming in the rat, but the time course, form, and magnitude of grooming are different with the different stressors [114].

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Such differences in response to specific stressors suggest that research involving the biobehavioral consequences of stress should be focused on those types of events that are most likely to serve as stressors across mammalian species, including humans. Social stress is a chronic or recurring factor in the lives of virtually all higher animal species. Disputes over resources often involve agonistic behaviors that result in wounding, exhaustion, and sometimes even death. Even for solitary species, spacing among individuals is based on avoidant behaviors that are seen to conspecific encounters, and agonistic interactions may be a direct follow-up when avoidance is slow or incomplete. Social stress, along with the stress of predation, has provided much of the impetus for the evolution of stress mechanisms. Both stressors are important, but the former is a constant in the lives of higher social animals and an intermittent event for solitary species, while predator stresses vary considerably across species.

2. Laboratory animal models of social stress

Animal models of social stress involve single, intermittent, or chronic exposure of a subject animal to a conspecific. The types of interactions that occur during conspecific encounters vary with the subject species, and the age, gender, and previous history of the individual, as well as the circumstances in which the exposure takes place. These interactions range from affiliative to agonistic and in the latter case may vary considerably in intensity, and in the polarization of aggressive or defensive behaviors between the two (sometimes more) interacting animals. Most laboratory studies of social stress effects utilize rodents, typically laboratory rats or mice, and sometimes hamsters. Although other species, notably primates, also serve as subjects of laboratory investigation of social stress effects, their social and stress-related behaviors are more commonly observed under seminatural conditions, or in the wild.

Adult males are the subjects of a great majority of social stress studies and of other research on animal models of stress-related psychopathologies [11]. In most mammalian species, male dominance hierarchies are much more visible than are the dominance relationships of females, as they tend to reflect overt fighting that may result in wounding and even in death. Moreover, male hierarchies tend to influence a wider range of behaviors than do those of females, with the latter typically emerging in a maternal care or protection context [120].

A number of different social stress situations are used in laboratory studies involving two or more animals in dyadic, group, or colony situations, respectively. In dyadic "social defeat" situations [108], there is a single confrontation or a series of confrontations separated by longer periods in which the stressed animal is returned to its home cage or left in a protected situation. The confrontations or the protected exposures may be repeated on successive tests. A variant involves intermittent defeat, in which animals are housed in adjacent areas within visual, auditory, and olfactory, but not tactile, contact. At intervals, the barriers between the two animals (in a variant, male–female pairs may be maintained on each side of the barrier [109]) are removed such that they can interact directly, establishing a victor and a defeated or submissive member of the pair. When the barrier is replaced, the defeated animal is left in chronic sensory (except for tactile) contact with the victor, such that its exposure to the psychosocial stressor is chronic, although the actual agonistic experience is intermittent. This procedure may involve animals that are initially naive [68] or, with one of them being an experienced fighter, in its own long-term enclosure [40,41], in which case it may be relatively certain that the other animal will be defeated.

Alternatively, animals may be grouped and maintained in colonies. The physical and social environments of such groups vary considerably, from seminatural habitats with tunnels and burrow systems including both male and female animals, to standard animal cages in which multiple animals of only one sex are housed. In general, the provision of larger and more natural habitats tends to produce higher levels of fighting [9]. Such a group may be left alone, typically with food and water constantly available, such that there is no specific provocation for the ensuing agonistic interactions, other than the presence of females, if these are present: Copulation increases aggression in male rats [32]. Agonistic behavior may be manipulated, however, by setting up social groups and later mixing them (Social instability models) or by introducing a selected high aggressive male into a stable social group (Social disruption model [95]).

All of these procedures provide animals with a history of defeat for comparison to controls. However, social instability models may blur the distinction between dominant and subordinate, or victorious and defeated animals, as all animals in such groups are likely to experience defeat when being moved from one group to another. Similarly, social disruption models involve defeat for all grouped animals exposed to the aggressive incomer, but this is combined with a history of victory or defeat within the group itself. Some but not all models also provide a victorious animal that can be compared to either losers or controls. However, when the victors have previous agonistic training or differential experience with the test situation, or when they have been selected on the basis of high aggressivity, such comparisons are confounded. For models in which all animals are randomly selected, initially naive and equally familiar or unfamiliar with the test situation, winning or losing may reflect individual differences factors for the two animals, such that comparisons following victory or defeat experience must also take into account the possibility of preexisting differences. These considerations apply in both dyadic or group social stress paradigms. However, in paradigms involving higher proportions of losers, as in

group or colony situations, a wider range of preexisting characteristics should be tapped within the loser category.

Two social stress paradigms that are significantly different in conceptualization from the above, in that they deemphasize the role of agonistic behavior, are crowding and social isolation. Properly speaking, crowding should refer only to studies in which animals are placed together in housing situations such that each has less than a standard amount of space. Since there is little information on what are the optimum or even reasonable space requirements for animals of most species, this is quite an arbitrary definition of crowding. In addition, ''crowding'' measured as animals per unit area may be quite different than ''crowding'' as number of interacting animals per housing unit. Crowding also implies that the mechanism of social stress is proximity, rather than agonistic interaction per se, and crowding stress studies may or may not involve attempts to measure agonistic reactions and to identify dominant and subordinate animals within the groups.

The use of social isolation as a stressor seems odd in view of the extensive use of social encounters as stressors. However, differences in social organization between species may make one or the other condition, isolation or grouping, particularly stressful. Sex differences may also be a factor. For rats, social grouping appears to be more stressful for males while isolation is more stressful for females [21,52]. Consonant with this difference, rat and mice females show relatively little within-sex fighting, as do females of most mammal species, although this may become more intense during the week or so following parturition [93]. In addition, although intersex altercations do occur, rat females are seldom wounded and show little subsequent avoidance of the male [17], suggesting that these encounters are not particularly stressful. Although highly aggressive or physiologically manipulated attacker male rats can be used to induce intense attack on females, it is difficult to compare the stress resulting from such attack to that of similarly attacked males, as the sexual size dimorphism of rats makes strong male attack on females potentially more dangerous than that of males on males.

A particular marker of social inhibition in females of many mammalian species is reduction of ovulation or other reproductive functioning while in social groups containing a dominant (reproductively active) female. The nonreproductive females may show few other signs of stress or distress. Nonetheless, the rapidity with which they may begin to cycle following removal of the dominant female makes it clear that this suppression is a response, albeit a very specific one, to the social hierarchy.

3. Markers of social stress

The diversity of social stress paradigms indicates a particular need for ways to evaluate the presence and perhaps even magnitude of social stress. One approach focuses on independent variables, examining those components of social interaction that are particularly relevant to the stress experience. Another emphasizes dependent variables, such as behaviors or physiological changes that may serve as relatively specific markers or indices of stress. With reference to the former, agonistic behavior is the major mechanism by which social experience is regarded as producing stress. For laboratory mice and rats, the most commonly used subjects of social stress laboratory research, agonistic behavior is a very obvious and salient component of most social grouping studies. It may be measured directly, in terms of fighting within each specific male dyad, or indirectly, in terms of wounds on the combatants.

The behaviors seen during agonistic interactions comprise two groups, one that may be used to infer victory, the other defeat. These have been intensively characterized in laboratory rats (e.g., Refs. [12,45–47]) and mice (e.g., Refs. [16,48]). Aggressive or offensive components include lateral attack, chase, and standing on top of, while flight/avoidance, defensive upright, and lying on the back are defensive elements. The defensive upright is typically regarded as a ''submissive'' posture and is widely used to indicate defeat [88,108]. However, this criterion for defeat may also reflect that the typical laboratory social stress test situation is so small as to make effective flight and escape impossible, forcing the animal to adopt a defensive posture that is seen primarily in inescapable situations.

The magnitude and the patterning of wounds on each animal also provide a valuable index of dominant–subordinate relationships, in that the dominant animal typically receives fewer wounds, and these tend to be located on its head and snout, whereas animals that are consistently the objects of offensive attack receive more wounds, and these are largely on the back. Other criteria may also be useful: In Visible Burrow System (VBS) studies, we use time on the ''surface'' (i.e., outside of the burrow system), weight loss, as well as wounding and (if these three indices do not agree) dyadic analyses of fighting behavior for each male dyad to determine dominance. In about 80% of cases, the three indices do agree perfectly, designating one male as the dominant in each colony. Number of wounds without reference to location appears to be a less reliable index.

With reference to physiological indices, the prototypical stress marker is activity of the hypothalamic–pituitary–adrenal (HPA) axis, typically measured as the level of cortisol or corticosterone (cort) in the plasma, saliva, or (less often) feces. While this marker is very consistent when male subjects are used, studies involving female primates in which only a dominant female is in reproductive condition often report that the reproductive female has higher circulating cortisol values than do females for which ovulation is suppressed. Other commonly used indices of stress are changes in relevant organs (e.g., increased adrenal weight) and weight loss during the stressful period.

4. Behavioral changes associated with social stress (victory/defeat)

4.1. Aggression and defense within the social situation

These represent a first set of behaviors to show relatively consistent and often long-term changes with defeat. Subordinate male rats in a VBS [11,13,17] or defeated male tree shrews [40,65,115] show reduced aggression, along with increases in avoidance of the area patrolled by the dominant; reduced activity and locomotion; immobility and sheltering in a place of concealment; and enhanced risk assessment. This last category, risk assessment, involves information-gathering activities concerning potential threat and includes scanning and (in rats) the assumption of low-back postures while cautiously approaching a threat stimulus [10]. Increases in particular defensive behaviors such as crouching, or the upright ''submissive'' posture, have also been reported after defeat in both rats and mice, and to predators as well as to the conspecific that defeated them [13,22,70,108]; as has risk assessment for subordinate Cynomolgous monkey females [105–107] and for dominant male sugar gliders, when moved to other groups where they became subordinates [74]. A particular point of interest is that subordinate rats that showed a failure of cort response to restraint (cort nonresponsive subordinates) showed less aggression, and more avoidance and crouching, than did subordinates that continued to be responsive [11,17].

4.2. Activity

Activity reductions are among the most commonly noted changes seen in subordinates and defeated animals. These have been reported in rats [13,81–83,101,112], tree shrews [37,40,115], and sugar gliders [74]. While clomipramine normalized the activity of defeated tree shrews [40], testosterone replacement did not [37].

4.3. Anxiety

Emotionality outside the agonistic context has been a particular focus of many stress studies. Social defeat has been shown consistently to enhance anxiety-like behavior in the elevated plus maze in rats [51,54,55,84,85,101]. However, Haller et al. [50] found that mild social stress normalizes the anxiety-like response of social isolates in the plus-maze task. Immobility elicited by ''sudden silence'' was increased after social defeat in rats [101], while cort nonresponsive subordinates showed enhanced immobility to handling and enhanced latency to right when turned over [17]. The situation in mice appears to be more complex, with reports that aggressive isolates or dominant grouped mice both show enhanced plus-maze anxiety [30] although social defeat enhanced anxiety in the same test [4]. These defeated mice also showed ''catatonic-like immobility'' and enhanced anxiety-like behavior in the open field, and in Porsolt's test [68]. Mice defeated in a ''minimal'' physical contact social defeat procedure showed more anxiety in the black–white test, but no change in a forced swim test [62].

Risk assessment measures outside the social situation showed a pattern similar to that of the more traditional anxiety measures, with two of three VBS groups (dominants and cort nonresponsive subordinates) showing enhanced risk assessment on a stretch attend apparatus [17] while subordinate male mice show enhanced risk assessment to social odors in their home cages [43]. In line with the somewhat anomalous finding of enhanced plus-maze anxiety for aggressive isolates and dominants, these same mice showed more risk assessment on the elevated plus maze [30].

The effects of social defeat on ultrasonic vocalization are consistent, with enhanced vocalization to startle stimuli [112,116,117].

4.4. Ethanol consumption

VBS colony subordinates show enhanced voluntary consumption of ethanol compared to dominants [14,15], as do pair-caged rats compared to controls [123]. Blanchard et al. [14] reported no reliable pregrouping consumption differences for animals that subsequently became dominant or subordinate. However, Wolffgramm and Heyne [124] did report that dominants drink less ethanol while isolated or housed in sensory contact with other rats. In mice, the phenomenon appears to be more variable, with subordinate C57BL/6J but not CBA/lac mice showing enhanced intake [69], nor did NMRI mice show enhanced intake after a ''minimal'' physical contact social defeat procedure [62]. In rhesus monkeys, rearing without the mother enhances ethanol consumption [57,58] as does isolation in controls [57].

4.5. Drug self-administration

Subordinate rats show enhanced intake of diazepam [124] and self-administration of cocaine [53,86,110]. However, social instability has been reported to decrease the enhanced self-administration of amphetamine seen when males cohabit with females [72]. Generalization between social stress and drug cues has been demonstrated for D-amphetamine [87] and pentylenetetrazole [118], suggesting that interoceptive effects of social stress may serve as a drug cue in self-administration situations. That these increases in drug self-administration are not part of a general pattern of enhanced consumption may be seen in studies indicating no differences in sucrose intake between dominant and subordinate CD-1 mouse females [89], and a general decrease in eating and drinking for subordinate male rats in VBS colonies [13].

4.6. Sexual behavior

Male dominance and sexual behavior appear to be strongly linked, with subordinate males showing less sexual behavior than dominants in a variety of species (albino mice [23], lesser mouse lemur [96,97], deer mouse [27], Long–Evans rat [13]). Subordinate males also show less scent marking (sugar glider [74], tree shrew [37,40]), and this reduction can be normalized by clomipramine [40] or by testosterone replacement [37].

In females, suppression of ovulation in subordinates (or, more generally, in females exposed to other females without explicit assessment of dominance) has been reported in a variety of species, including naked mole rats [29], Djungarian hamsters [49], mice [75], Damaraland mole rats [6], and marmosets [5,102]. This suppression appears to be very sensitive to sensory contact with the dominant females: Subordinate females removed from contact with the female ovulated in 10 days but those in contact with the dominant's scent ovulated in 30 days [5].

4.7. Social behaviors

In addition to the enhanced defensiveness and reduced levels of aggression shown in interactions with dominants and others in the test situation, subordinate or defeated animals show a variety of changes in other aspects of social behavior. They show less social contact (rats [13,82]) and are less affiliative (Cynomolgous females [105–107]). Subordinate mice prefer the odor of unfamiliar females, but among dominant odors prefer that of familiar rather than strange dominants [99]. As this suggests, subordinates appear to be particularly attentive to the dominant and its behaviors. During the late luteal phase of the female dominant (a period when the dominant is more defensive), nondominant female vervet monkeys show more aggression [98]. In subordinate hamsters, presence of the dominant reduces brain self-stimulation [71]. A particularly interesting finding is that, in macaques, subordinates appear to reduce competitive behaviors in the presence of the dominant, ''playing dumb'' when tested with the dominant although showing no learning differences when tested apart [28]. Similarly, subordinate macaques tend to lose a ''tug of war'' for food with the dominant when separated from it by only 30 cm, a difference that disappears with 100-cm separation [103].

4.8. Learning and memory

Subordinate tree shrews show decrements in memory that appear to be restricted to types of memory that are mediated by the hippocampus [66,91]. These memory deficits are not in temporal sequence with the increases in cortisol that occur during stress–no stress periods [92]. An additional indication that cortisol is not the major mechanism of stress effect on learning/memory systems is provided by reports that although social stress causes spatial learning deficits, a similar but artificial elevation of cortisol only mildly affects the same learning measures [66].

5. Neurotransmitter/modulator changes associated with social stress (victory/defeat)

5.1. Serotonin

The transmitter system most widely studied in the context of social stress is the serotonergic system. Serotonin neurotransmission has been shown to be altered by a variety of laboratory stressors, and serotonin (5-hydroxytryptamine, 5HT) also plays a role in mediating many of the behaviors that contribute to and are affected by social status, including aggression and sexual behavior. The majority of studies suggest that 5HT systems are activated in response to social stress. Examination of tissue concentrations of 5HT and its metabolite, 5-hydroxyindole acetic acid (5HIAA), has shown elevated concentrations of 5HIAA and/or increased 5HIAA/5HT ratios in various brain regions of subordinate rats and mice, suggesting increased serotonergic activity [7,10,59]. In addition, adult golden hamsters that had been socially defeated during puberty had increased 5HT innervation of lateral septum and anterior hypothalamus, suggesting that defeat led to an increase in the capacity to release 5HT in these areas [26]. Subordinate talapoin monkeys also had elevated levels of 5HIAA in their cerebrospinal fluid, which may reflect increased 5HT neurotransmission in the brain [126].

Both pre- and postsynaptic receptors and transporters for 5HT have been shown to be altered by social stress. Perhaps the most consistent findings are a stress-related increase in binding to $5HT_{2A}$ receptors in cortex and a corresponding decrease in $5HT_{1A}$ receptors in hippocampus [7,34,79]. In addition, in the VBS model, binding to presynaptic $5HT_{1A}$ autoreceptors is preferentially downregulated in the median raphe of subordinate animals [78]. In the VBS model, all VBS-housed animals show a similar decrease in 5HT transporter binding, with the most pronounced effects occurring in the dominant animals [80]. The dominant animals do appear to be somewhat stressed compared to the pair-housed controls, suggesting that the downregulation of 5HT transporters may be part of an adaptive response to mild social stress; this interpretation is supported by the observation that a single social defeat is sufficient to decrease binding to the 5HT transporter in hippocampus [8].

The functional effects of the changes in 5HT receptor binding are unclear. Defeated rats exhibit a blunted cort response to the $5HT_{1A}$ agonist 8-OH-DPAT, suggesting a functional subsensitivity of these receptors — a result that corresponds well with the observed decrease in receptor number [64]. However, in Cynomolgous monkeys, the hormonal responses to the 5HT releaser fenfluramine did not differ between dominant and subordinate animals,

indicating no differences in postsynaptic sensitivity to nonselective stimulation of 5HT transmission [18,105].

5.2. Norepinephrine

The effects of chronic social stress on both pre- and postsynaptic elements of noradrenergic neurotransmission have been studied in both rat and tree shrew models of psychosocial stress. Subordination stress selectively increased expression of the gene for tyrosine hydroxylase (TH), the rate-limiting enzyme in catecholamine synthesis, as indicated by a selective increase in TH mRNA in noradrenergic, but not dopaminergic, brain regions; furthermore, the increased mRNA levels in locus coeruleus were accompanied by a corresponding increase in immunoreactive TH protein [20,122]. Since several different stress paradigms have shown that the locus coeruleus noradrenergic system is activated by stress, the changes in TH are likely to reflect an upregulation of synthetic capacity as a result of increased neuronal activity and transmitter release.

Stress-induced changes in adrenergic receptors have been studied in depth in the tree shrew model. After 10 or 21 days of social stress, α_2-adrenoceptor binding was downregulated in the subordinates compared to controls in several brain regions [36]. Time course studies indicate that the number and affinity of these receptors are regulated in distinct temporal patterns within individual brain regions [33]. Beta-adrenergic receptors are also regulated in a similarly complex manner in this model, with upregulation of β_1- and β_2-adrenoceptors in the pulvinar nucleus but downregulation of these receptors in cortex and hippocampus after 28 days [35]. In addition, the binding affinity of β-adrenergic receptors was decreased in cortex and hippocampus following 21 days of psychosocial stress. These complex changes in regional populations of adrenergic receptor subtypes indicate that the function of various noradrenergic circuits may be differentially regulated in response to chronic stress; furthermore, this regulation may occur via changes in receptor turnover, synthesis, and conformation.

5.3. Dopamine

Unlike serotonin and norepinephrine, dopamine has only recently been considered to be a stress-responsive neurotransmitter. As a result, studies focusing on the effects of social stress on dopaminergic systems are relatively rare. Although in one mouse study dominants did have lower brainstem dopamine content than subordinate or control animals [59], in monkey and rat social hierarchies, tissue content of dopamine and its metabolites was unaffected by rank [10,38]. Similarly, social stress had no effect on the regulation of TH in dopaminergic nuclei, in contrast to the increase in TH mRNA and protein seen in noradrenergic nuclei [122].

Dopaminergic neurotransmission is not completely unaffected by social stress, however. Exposing previously defeated rats to the threat of defeat elicits an increase in extracellular dopamine in both the prefrontal cortex and the nucleus accumbens, as measured using in vivo microdialysis [110,111], indicating that these limbic areas are responsive to stimuli associated with social stressors. In addition, binding and function of the D_2 dopamine receptor subtype have been shown to be decreased in socially subordinate female Cynomolgous monkeys. These animals have decreased D_2 receptor binding capacity in the basal ganglia, as indicated by PET scanning after injection with ^{18}fluorocleboprid; in addition, the subordinates exhibited a blunted prolactin response to the D_2 antagonist haloperidol, indicating a functional subsensitivity of these receptors [105,106].

5.4. Amino acid transmitters

Very few studies have examined the effects of social stress on components of excitatory amino acid neurotransmission. However, Krugers et al. [67] found that a single social defeat was sufficient to lead to an increase in the ratio of NMDA to AMPA receptors in the hippocampus CA3 area of rats. The altered receptor ratio may alter the physiological actions of synaptically released excitatory amino acids, since the two receptor subtypes differ in their kinetics, ion permeability, and voltage dependence.

The subunit composition of receptors for the inhibitory amino acid GABA is also affected by social stress, as mRNA levels of both α_1 and γ_2 $GABA_A$ subunits are increased in cortex following social defeat [61]. In comparison, no changes in subunit mRNA levels were observed in the brains of the resident animals that defeated the intruder mice. The increase in subunit expression is likely to reflect a general upregulation of the $GABA_A$ receptor, but it may also indicate changes in the subunit composition, and thus the electrical and pharmacological properties, of the receptors.

5.5. Corticotropin-releasing factor (CRF) and vasopressin

CRF and arginine–vasopressin (AVP) are known to be involved in the initiation and modulation of HPA axis activity; in addition, extrahypothalamic CRF and AVP circuits have been implicated in the mediation of stress-related and social behaviors, respectively. As a result, the effect of social stressors on the expression and release of these two neuropeptides has been studied in a variety of animal models. Social subjugation either in adulthood or in puberty led to reduction in AVP stores in anterior hypothalamus of hamsters, suggesting decreased AVP release within this brain region which is involved in aggressive behavior in this species [26,31]. Conversely, measurement of AVP in samples collected using in vivo microdialysis indicates that social defeat enhances release of this peptide in another area of the hypothalamus, the paraventricular nucleus (PVN), where it is believed to play a role in

modulation of the HPA axis response [125]. Similarly, AVP immunoreactivity was increased in the zona externa of the median eminence (ZEME), a projection area of neurons originating in the PVN in subordinate colony-housed male rats, suggesting enhanced transport of AVP to the terminal fields [24].

In the VBS model, chronic social stress impacts mRNA for AVP and CRF. Messenger RNA levels for AVP were unaffected by social stress in the PVN; however, AVP mRNA was significantly decreased in the medial amygdala and mRNA levels in this region correlated significantly with plasma testosterone titers, suggesting that the changes in AVP were a secondary effect of stress-induced suppression of gonadal hormones [3]. Mixed-sex housing in the VBS also increased CRF mRNA in PVN in both the dominants and stress-responsive subordinates, perhaps a consequence of repeated HPA axis activation. In addition, CRF mRNA was increased in the central amygdala of the subordinates, suggesting activation of extrahypothalamic CRF circuits, which are believed to mediate certain stress-related behaviors.

The regulation of the receptors for CRF has been examined in the tree shrew model of social stress. After 24 days of psychosocial stress, subordinates show a down-regulation of CRF receptors in brain regions involved in HPA axis regulation, including the anterior pituitary, dentate gyrus, and CA1–CA3 of hippocampus [39]. Conversely, the number of CRF binding sites was increased in other areas of the brain, including the frontal and cingulate cortex, the claustrocortex, the central and lateral nucleus of amygdala, and the choroid plexus. However, in all regions except the claustrocortex and the central amygdala, the increase in receptor number was partially offset by a decrease in binding affinity.

Overall, it appears that social stress activates the CRF circuits that are directly associated with activation and regulation of the HPA axis; an apparent increase in presynaptic activity is accompanied by a corresponding down-regulation of the postsynaptic elements. In contrast to CRF, evidence from both hamsters and rats indicates that subordination and defeat inhibit the extrahypothalamic AVP circuits involved in aggressive and sexual behavior. Finally, while CRF mRNA is upregulated in extrahypothalamic areas, the net effect of social stress on CRF neurotransmission in these area is less clear, since the number and affinity of the postsynaptic receptors are altered in a complex manner.

6. Other

Galanin, a 29-amino-acid neuropeptide, can be found in approximately 80% of the TH-containing neurons in the locus coeruleus. Chronic subordination in the VBS leads to an increase in mRNA levels of preprogalanin in the locus coeruleus of the subordinate animals [60]. The levels of mRNA were positively correlated with the number of wounds per animal and negatively correlated with body weight gain, suggesting that the degree of galanin gene expression was associated with the severity of the stress. The increase in preprogalanin mRNA in the subordinate animals parallels that observed in TH mRNA in this region (see above), indicating that the two mRNAs may be upregulated in tandem as a result of a stress-induced increase in the activity of locus coeruleus neurons.

In addition, mRNA levels of proopiomelanocortin (POMC), the precursor to ACTH and β-endorphin, were increased in the anterior pituitary of VBS subordinate rats [20]. Again, the magnitude of the response correlated with wounding and weight loss, and also adrenal weight, suggesting that the POMC response reflected stressor severity and the degree of HPA axis activation.

7. Neuronal structure/survival changes associated with social stress (victory/defeat)

Several studies have indicated that chronic stress affects neurons in the hippocampal formation in a variety of ways, leading to alterations in dendritic morphology, cell survival, and neurogenesis. A recent examination of the morphology of hippocampal neurons has found significant shrinkage of the apical dendritic arbors of CA3 pyramidal neurons in all animals housed in the VBS [80]. The observation, that these changes occur to a similar (or greater) extent in dominants as well as in the more severely stressed subordinates, suggests that dendritic remodeling may be a common response to chronic activation of the HPA axis that does not vary significantly with the severity of the stressor. Similar dendritic remodeling has been observed in the hippocampus of subordinate tree shrews [73]. These dendritic changes were accompanied by alterations in the chromatin structure within the nucleoplasm of CA1 and CA3 pyramidal cells although there were no signs of neuronal degeneration or cell loss [42,119]. Although neuronal survival is not significantly altered in this model of psychosocial stress, neurogenesis does appear to be inhibited within the dentate gyrus of subordinate tree shrews compared to controls [44].

Far more pronounced pathological changes were found in the hippocampus of vervet monkeys that died spontaneously at a primate center in Kenya. These animals exhibited signs of severe stress, such as gastric ulcers and enlarged adrenals, and several also showed evidence of social conflict, such as bite marks. When compared to animals euthanized for other reasons, the stressed monkeys showed evidence of neurodegeneration in Ammon's horn, especially in CA3 [113]. However, it must be noted these animals are presumed to have died from stress-related causes, which indicates a severity of stress much greater than that seen in most other social stress paradigms.

8. Summary and discussion

In humans, social stress is viewed as a major [90] etiological factor in the development of a number of emotional disorders, including depression and anxiety (e.g., Ref. [63,94]) and substance abuse [19]. It may also impact immune functioning [2], heart disease [56], and male (e.g., Ref. [77]) and female [121] reproduction. Although social stress in people may respond to a number of life events, low social status may be regarded as a particularly important index of stress. Low social status typically involves reduced access to resources, safe living conditions, and health care. However, these material resources problems do not appear to account entirely for the effects of low social status, as the meaning assigned by the individual to his/her status with reference to others may provide stress that is additional to (or interactive with) the material consequences of low status [25]. The cognitive/emotional elements implied by this concept are difficult to evaluate in animal models, and may or may not have similar impacts in nonhuman mammals as in humans. Nonetheless, the results of social stress research in nonhuman mammals do indicate a wide range of behavioral and physiological effects of defeat or subordination, along with suggestions that stress-ameliorating factors such as social support may prove beneficial in the animal models as well. These findings suggest that defeat and subordination may provide particularly relevant and powerful approaches to analysis of the dynamics of social stress effects in people.

In animal models, social stress leads to a variety of behavior changes, particularly involving emotionality-linked behaviors such as anxiety, defensiveness, and substance self-administration, as well as social and sexual behaviors. It also produces many changes in the brain, affecting neuronal structure and survival as well as neurochemical transmission. Overall, social stress, like other stressors, induces a net stimulation of serotonergic and noradrenergic neurons, although the functional outcome of increased transmitter release is likely to be modulated by region- and time-specific changes in receptor populations. Although few studies have been conducted examining the effects of social stress on other classical transmitter systems, it has been shown to modify various aspects of dopaminergic, GABAergic, and excitatory amino acid transmission. In neuropeptide systems, CRF and AVP pathways involved in the HPA axis response appear to be activated by social stress, while extrahypothalamic AVP and CRF circuits are inhibited and stimulated, respectively. Chronic social stress has been shown to alter the morphology of hippocampal neurons, which may affect learning and memory processes in these animals, consonant with findings that hippocampally mediated learning and memory are indeed reduced in subordinates. Finally, although the effects on hippocampal pyramidal cell survival are equivocal, chronic subordination has been shown to retard neurogenesis within the dentate gyrus. Together, these results indicate that social stress can have profound consequences on the brain; further study is needed to determine which of these changes are adaptive and which are associated with pathological changes in brain function and behavior.

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