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Long-lasting stress sensitisation

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Abstract

Stressful experiences in humans can result in a spectrum of long-term changes in behavioural, autonomic and hormonal responsivity. An extreme form of such alterations is found in patients with post-traumatic stress disorder (PTSD). A number of animal models has been developed in which intense stressful experiences (shocks, social confrontations) result in longterm altered responsivity of behavioural, autonomic and hormonal responses to aversive challenges which mimic many of the changes seen in PTSD. These models of stress-induced sensitisation are beginning to generate a better understanding of the vulnerability factors, time-course and underlying neuronal substrates of the long-term disturbances experienced by humans as a result of stressful life events.

Keywords: Behaviour; Autonomic response; Endocrine response; Anxiety; Affective disorder; Post-traumatic stress disorder (PTSD); (Rat)

1. Introduction

Any novel or threatening environmental stimulus activates stress-systems in brain and periphery and induces changes in behaviour. This stress response is meant to maintain or restore control. The brain is not only the site where the stress response is initiated and coordinated, but also a target of activated-neural and hormonal-stress systems. Thus, neuro-adaptations triggered by stress-mediators (neurotransmitters, neuropeptides, hormones) constitute the prime mechanism for modification of existing and acquisition of new behavioural strategies, thereby optimising the adaptive capacity of the organism and increasing its future chances of control (De Wied and Croiset, 1991).

The nature of stress-induced neuro-adaptations appears to depend on the controllability of the stressor (Huether, 1996; De Kloet and Joëls, 1999). Controllable challenges generally activate mechanisms that facilitate consolidation of ongoing behaviour, and repeated exposure to the same controllable stressor will therefore lead to habituation of the neuroendocrine stress response. Exposure to an uncontrollable stressor, however, can induce an increase in the behavioural and neuro-endocrine responses following repeated exposure to the same stressor. When its intensity is high enough, uncontrollable stress can sensitise responses to a wide variety of stimuli that are unrelated to the initial stressor for a long period of time. Even a single, brief but intense stress experience can lead to such generalised sensitisation of stress responses.

Generalised stress sensitisation can be viewed as a pro-adaptive response. It likely represents an ultimate attempt of the organism to facilitate development of new behavioural strategies given the fact that the existing ones have proven inadequate to cope with the actual, stressful, environmental demands. When this attempt proves futile, however, increased responsiveness will result in frequent and excessive activation of stress systems in daily life. This condition of maladaption is generally thought to be a precursor of a variety of pathologies. Stress sensitisation in experimental animals can therefore yield useful models for human stress-related psychiatric and psychosomatic diseases. The present paper gives a brief review of the current literature with regards to generalised stress sensitisation in animals as a model for psychopathology, in particular post-traumatic stress disorder (PTSD).

This review is written in honour of David de Wied, who dedicated his scientific life to the study of the role of

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neuropeptides and hormones in stress-adaptation. The authors are proud to belong to his scientific offspring, and are grateful for his wisdom and friendship.

2. Sensitisation and human pathology

Extraordinary stressful experiences can have long-lasting consequences for psychological and physiological functioning in humans (Boscarino, 1997). The extent to which normal function will be perturbed depends on genetic background, gender, life exposure to stressful life events and their quality and intensity (True et al., 1995; Watson et al., 1998; Breslau et al., 1999). Various psychiatric conditions (generalised anxiety disorder, panic disorder, affective disorders) can be associated with stressful life events and patients will often meet criteria for more than one diagnosis at the same time (Friedman and Yehuda, 1995). Nevertheless, this review will focus mainly on PTSD, since it probably represents an extreme case in a spectrum of stress-related long-term changes, its etiology is clearer and more homogeneous than that of other anxiety and affective disorders, and animal models are available that mimic a number of its key features.

PTSD is a cluster of long-lasting symptoms following extreme stressful life events such as threat to life or physical integrity, including recollections, emotional numbing, conditioned fear responses and psychological and physiological hyperarousal (DSM-IV, 1994). Although the conditional risk after trauma exposure is only 9%, lifetime prevalences in the general population are in the order of 5% for men and 10% for women (Breslau et al., 1998; Solomon and Davidson, 1997). The main behavioural disturbances contain elements of intrusive (but not necessarily stimulus-evoked) memories, strong conditioned fear responses to trauma-related stimuli, and increased startle responses to stimuli. There has been some debate whether non-trauma-related stimuli also evoke psycho-physiological hyperreactivity, since some "neutral" stressful challenges in the laboratory generate similar responses in patients and controls (Casada et al., 1999). However, these may not mimic less predictable and more threatening stimuli in daily life, and there is firm evidence for exaggerated acoustic startle responses in abused women with PTSD (Morgan et al., 1997), not just in veterans where an element of classical conditioning cannot be excluded (Morgan et al., 1996).

While there is little evidence to support baseline changes in catecholaminergic function (Southwick et al., 1995), more recent pharmacological challenge paradigms have shown hyperreactivity to both presynaptic α_2-adrenoreceptor blockade and postsynaptic serotonergic agonists (Southwick et al., 1997). Altered basal levels of hormones from the hypothalamo–pituitary–adrenal axis, including evidence for elevated cerebrospinal fluid levels of corticotropin-releasing hormone (CRH) (Bremner et al., 1997b), are also seen in a number of other psychiatric disorders, but other changes seen in PTSD patients seem to reflect a relatively specific disturbance characterised by low basal plasma cortisol, a more pronounced circadian rhythm, and enhanced suppression of cortisol levels by exogenous dexamethasone (Yehuda et al., 1996; Stein et al., 1997b). Thyroid abnormalities, reflected in higher basal levels of plasma thyroxine and triiodothyronine, also seem relatively specific for PTSD (Mason et al., 1995) and correlate with hyperarousal scores (Wang et al., 1997). More recently, evidence has emerged for low baseline and panickogen-stimulated plasma levels of neuropeptide Y (Rasmusson et al., 2000) and increased psychological responsivity to cholecystokinin (Kellner et al., 2000), indicating that a variety of central nervous system (CNS) neuropeptide systems show alterations in PTSD. Evidence for somatic disturbances in traumatised patients has emerged for the immune (Boscarino and Chang, 1999), cardiovascular (Orr et al., 1998) and gastrointestinal (Irwin et al., 1996) systems. The latter domain includes increased visceral pain perception typical of functional bowel disorders (Stam et al., 1997), but other chronic pain syndromes are also highly prevalent in PTSD (Beckam et al., 1997). Perhaps paradoxically, there are also indications for increased stress-induced analgesia (Pitman et al., 1990) and increased cerebrospinal fluid levels of β-endorphin (Blaker et al., 1997) in veterans with PTSD.

Research into neuroanatomical changes and functional imaging of the CNS in patients is still in its infancy. There is some evidence for decreased hippocampal volume in different PTSD groups (Bremner et al., 1995; Stein et al., 1997a), and for lower neuronal density in medial temporal structures (Freeman et al., 1998), but it is not yet clear whether such abnormalities are necessarily consequences of traumatic experiences or pre-existing factors that increase vulnerability. Parietal cortical blood flow during auditory performance tasks correlates negatively with poor attention (Semple et al., 1996), and general PTSD symptom severity with caudate flow (Lucey et al., 1997). Both conditioned responses to trauma-related stimuli (Bremner et al., 1999; Liberzon et al., 1999) and to administration of an α_2-adrenoceptor antagonist (Bremner et al., 1997a) result in differential activation of prefrontal, orbitofrontal, temporal and parietal cortices in PTSD patients and controls. In one study, activation of the amygdaloid area by such stimuli was seen in patients, but not controls (Liberzon et al., 1999). More studies involving general, non-trauma-related stressful stimuli need to be performed to assess the generality of altered CNS activation patterns.

3. Animal models

A rich literature is available on the effects of chronic heterotypic or chronic variable stressors on subsequent

stress responsivity in laboratory animals. Perhaps more relevant for long-lasting changes of major stressful life events in humans are animal models involving relatively brief and infrequent exposure to intense stress. If these models are to have relevance for posttraumatic changes, they should meet at least some of the following criteria: even relatively brief stressors should be able to induce both behavioural and physiological sequellae of PTSD; the effects should be dose-dependent and persist or increase in time; there should be a potential for bi-directionality of long-term effects and for individual differences in vulnerability as a function of genetics and prior experience (Yehuda and Antelman, 1993). There are a number of rat models using environmental stressors that meet a large proportion of these criteria.

In the classic model of "learned helplessness", effects of daily sessions of 80–135 brief electric shocks on avoidance-escape behaviour and open field activity last at most a few days (Weyers et al., 1989; Maier et al., 1979). Paradoxically, much longer lasting effects are found when much fewer shocks are concentrated in a short period of time (Murison and Overmier, 1998). Since its first description in the early seventies (Levine and Madden, 1973), this model of long-term sensitisation after a short session of foot shocks has been extensively validated. It can cause altered reactivity (both hypo- and hyper-responsivity) in a wide range of novel challenges that can last for months, and is indicative of increased anxiety and startle responsivity (Van Dijken et al., 1992a,b; Servatius et al., 1994). The sensitisation process can be counteracted by treatment with classical anxiolytics, but much less by antidepressants (Van Dijken et al., 1992c, Bruijnzeel et al., unpublished). Evidence for sensitisation of autonomic responses (gastrointestinal, cardiovascular) that can be expressed independently from behavioural sensitisation has emerged more recently (Stam et al., 1996; Bruijnzeel et al., 1999b).

A social defeat by an aggressive conspecific, either single or repeated on several days, also causes long-term changes in responsivity. The increased immobility response to some novel stressors is similar to that seen in the foot shock model (Koolhaas et al., 1990). Disturbances in circadian rhythms of heart rate, core temperature and activity seem more specific for this model (Meerlo et al., 1996; Harper and Tornatzky, 1996), as we have found no evidence for similar disturbances in foot shocked rats (Stam et al., unpublished). Interestingly, the long-term disturbances become less pronounced when animals are housed in groups rather than singly after defeat (Ruis et al., 1999), or when subjects show more aggressive behaviour during the interaction (Meerlo et al., 1999). In contrast to the foot shock model, defeated rats show increased immobility in the Porsolt swim test, which can be reduced by an antidepressant (Koolhaas et al., 1990).

Long-term sensitisation can also occur after social confrontations that do not have the disadvantage of physical wounding during the encounter. Rats that are forced to witness another rat being shocked show long-term changes in behavioural reactivity that have the opposite direction of that seen in the shocked rats, i.e. increased activity in a novel environment. That different substrates underlie these different behavioural responses is evident from the fact that they are reversed by an opiate antagonist in the witness group, but not in the shock group (Van den Berg et al., 1998). Interestingly, long-lasting tolerance to the analgesic effect of morphine has been reported in socially defeated rats (Miczek, 1991), indicating that modulation of endogenous opioid systems may also be involved in other sensitisation models. In a similar model, rats exposed to the threat of a cat from a shielded compartment show lasting increases in anxiety-like behaviour in the elevated plus maze and holeboard test (Adamec and Shallow, 1993). Subsequent work has shown that this predator exposure also causes increased startle responses to noise (Adamec, 1997) and lateralisation of sensitisation of the neuroanatomical substrates involved (Adamec et al., 1999).

Finally, it has become clear that administration of drugs (usually psychostimulants) to laboratory rats can cause time-dependent sensitisation that is probably a function of their non-specific, stressful nature (Sorg and Kalivas, 1995). This is underlined by the fact that there is cross-sensitisation between both a stress challenge after previous drug administration (Hamamura et al., 1997), and a drug challenge after a previous stressful experience (Diaz-Otanez et al., 1997). Indeed, repeated intra-cerebroventricular administration of CRH has similar sensitising effect on later responsivity to amphetamine (Cador et al., 1993). Interestingly, in the light of co-existing hyperarousal and numbing symptoms in PTSD, evidence has also emerged in these models for bi-directionality of expression. A low intensity stressor can cause an increase, and a high intensity stressor a decrease in later cataleptic responses to haloperidol (Antelman et al., 1991), while an oscillating pattern of cocaine-induced neurochemical sensitisation to amphetamine has been reported with certain cocaine administration regimens (Antelman et al., 1997).

Taken together, there is good reason to assume that animal models of stress-induced, time-dependent sensitisation mimic a number of key aspects of long-term disturbances following extreme life events in humans. They show construct validity in causing stabile, long-term changes after brief but intense stressful life events, face validity since the alterations in behavioural reactivity, hormonal and autonomic function show many parallels with those in PTSD, and at least some predictive validity in the modulating effects of anxiolytics and antidepressants on symptoms.

4. Autonomic responses

In addition to behavioural sensitisation, a single stressful event can also induce long-term alterations in physio-

logical responsiveness to novel stimuli. In a recent study (Bruijnzeel et al., 1999b), we investigated the long term effects of a single footshock experience on cardiovascular responsivity. All three challenges used, that is the novel cylinder test, the shock prod acquisition test (electrified prod inserted in the home cage) and the shock prod retention test (non-electrified prod inserted one day later), showed sensitisation of the blood pressure but not the heart rate response 2 weeks after the footshock experience. This is in accordance with our previous results that, in the home cage prod test, behavioural sensitisation is not expressed while rats do show sensitisation of colonic motility and brain Fos responses (Bruijnzeel et al., 1999a; Stam et al., 1996). Also, repeated i.p. injections with amphetamine sensitise mean arterial pressure, heart rate and locomotor responses to subsequent injections with amphetamine, whereas i.c.v. amphetamine sensitises behavioural responses without affecting cardiovascular responses (Yoshida et al., 1993). Together, this indicates that sensitisation of behavioural and autonomic responses can be expressed independently, and that their expression depends on the nature of the challenge.

Social stimuli can also induce long-lasting alterations in autonomic parameters. Following social defeat, rats display a decrease in the amplitude of the circadian rhythms of heart rate and body temperature due to an increase in basal heart rate and temperature during the light phase, when rats are resting (Tornatzky and Miczek, 1993; Meerlo et al., 1997). However, it is not known yet whether social defeat can induce long-term alterations in autonomic responsivity to novel challenges, as has been found following exposure to a single session of inescapable footshocks (Bruijnzeel et al., 1999b; Stam et al., 1996).

5. Hormonal responses

It is well known that chronic or frequent stress can have long-lasting effects on the hypothalamo–pituitary–adrenal-axis and other hormonal systems. Recent evidence indicates that this also holds for single, brief stressful events. A single footshock experience sensitises the adreno-corticotropic hormone (ACTH) response to a novel noise challenge, and both the ACTH and the corticosterone response to amphetamine assessed several weeks later (Van Dijken et al., 1993; Vanderschuren et al., 1999). Increased release of [Arg^8]vasopressin (vasopressin) may underlie this sensitisation of the hypothalamo–pituitary–adrenal-axis, since vasopressin stores were found to be increased in the external zone of the median eminence where fibers of CRH neurons located in the parvocellular paraventricular nucleus of the hypothalamus terminate on portal vessels (Van Dijken et al., 1993). Stressful stimuli are known to specifically upregulate vasopressin hnRNA and mRNA in these CRH neurons (Bartanusz et al., 1993; Ma et al., 1997), and vasopressin can potentiate the CRH-induced release of ACTH from corticotrophes in the pituitary (Kovacs, 1998). The hypothesis that the long-term changes in vasopressin depend on the ability to acutely stimulate the hypothalamo–pituitary–adrenal-axis was tested. A single injection with interleukin-1ß sensitises the ACTH and corticosterone response to interleukin-1ß 11 days later and to an amphetamine challenge 3 weeks later (Schmidt et al., 1995, 1999), and also induces a long-term increase in vasopressin stores in the median eminence (Schmidt et al., 1996). In contrast, exposure to two short episodes of social defeat does not upregulate vasopressin or CRF stores, and induces temporal dynamic changes in hypothalamo–pituitary–adrenal regulation suggestive of increased feedback inhibition (Buwalda et al., 1999). Moreover, neither ether nor insulin stress affects vasopressin stores (Schmidt et al., 1996). The results suggest that qualitative characteristics of the stressor, rather than its capacity to stimulate the hypothalamo–pituitary–adrenal-axis alone, are important determinants of its long term effects on co-expression of vasopressin in CRH neurons.

Recent data indicate that a single footshock experience also induces long-term alterations in the hypothalamus–pituitary–thyroid axis. In female U:RP rats basal total thyroxine (T4) levels are decreased 3 weeks after foot shock stress (Bruijnzeel, unpublished). In a second study, we found a decrease in free T4 levels and a tendency to a decrease in total T4 levels in preshocked male and female Wistar (U:WU) rats (Stam et al., 1999). In PTSD patients, an increase in total T4 levels has been reported (Mason et al., 1995). These opposite findings could be the result of a species dependent effect of stress on the hypothalamus–pituitary–thyroid-axis. In rodents, stress generally causes a decrease, and in primates, an increase in thyroid activity (Mason and Mougey, 1972).

6. Neurochemical responses

To gain more insight in the neuronal networks underlying stress-induced sensitisation, we studied the effect of a single session of inescapable footshocks on the expression of Fos in a wide variety of brain areas after a shock prod challenge in the home cage 14 days later. Fos, the protein product of the proto-oncogene c-*fos*, was used since it is a non-specific marker for neuronal activation (Morgan and Curran, 1995), and the number of Fos positive cells is dependent on the intensity of the stimulus (Campeau and Watson, 1997). Preshocked rats showed sensitisation of Fos expression in brain areas involved in anxiety and fear and in neuroendocrine and autonomic control, including the prefrontal cortex, the paraventricular nucleus of the hypothalamus and the locus coeruleus. Interestingly, the preshock experience also sensitised the Fos response in the

nucleus accumbens core and shell, brain areas intensively studied for their potential role in drug abuse (Wickelgren, 1997).

Stressful stimuli activate noradrenergic neurons in the locus coeruleus and dopaminergic neurons in the ventral tegmental area, and the role of these systems in stress effects has been focus of extensive research. Via their central projections, the noradrenergic neurons of the locus coeruleus modulate the activity of a wide range of cortical and limbic brain areas that are involved in behavioural, neuroendocrine and autonomic control (Foote et al., 1983). Dysfunction of these neurons likely plays a role in anxiety disorders, including PTSD (Charney and Deutch, 1996). The dopaminergic neurons in the ventral tegmental area most prominently project to the nucleus accumbens and the frontal cortex, and they are activated by aversive as well as by rewarding stimuli (White, 1996; Piazza and Le Moal, 1997). The responsivity of these noradrenergic and dopaminergic systems to novel challenges is dependent on the stress history of the organism. In rats, a single tail-shock session induces an enhanced release of dopamine and noradrenaline in the medial prefrontal cortex and of noradrenaline in the hippocampus, and previous exposure to chronic cold stress sensitises these responses without affecting the basal release (Gresch et al., 1994; Nisenbaum et al., 1991).

Psychostimulants such as amphetamine and cocaine can induce long-lasting sensitisation of neurochemical (dopamine release in the nucleus accumbens) and behavioural responses to subsequent challenges. Rats exposed to two injections with amphetamine display an enhanced behavioural response to amphetamine until at least 4 weeks later (Magos, 1969). Moreover, exposure to a single injection of amphetamine induces a long lasting sensitisation of amphetamine-induced release of dopamine in the nucleus accumbens. Interestingly, the results of Kolta et al. (2000) show that the amphetamine-induced stereotyped behavioural response increases over time after the initial injection with amphetamine. Three days after pretreatment with amphetamine rats display a sensitised stereotyped behavioural response to amphetamine compared to saline, and a more pronounced stereotyped response to amphetamine is found 15 and 30 days after pretreatment. Gradual development in time is not a feature specific for pharmacological sensitisation, since it has also been found for behavioural sensitisation induced by a single session of footshocks. Preshocked rats display an enhanced immobility response 1 day after exposure to the footshocks when placed in a novel environment, and this response increases over time (Van Dijken et al., 1992a).

Since the demonstration that stress and amphetamine are interchangeable with regard to behavioural sensitisation (Antelman et al., 1980), research has focussed on the underlying neuronal mechanisms and the effects of stress on the vulnerability to drugs of abuse. It has been shown that pretreatment with 5 days of footshock stress sensitises the cocaine-induced increase in extracellular dopamine levels in the nucleus accumbens (Sorg and Kalivas, 1991). Daily sessions of emotional stress (witness of a conspecific being shocked) but not of footshock stress on 5 consecutive days enhance the initiation of i.v. self-administration of morphine and cocaine and ventral tegmental intracranial electrical self-stimulation in rats (Ramsey and Van Ree, 1993; Kuzmin et al., 1996). Moreover, social defeat directly followed by threat for 4 consecutive days increases the amount of cocaine self administration and defeated rats acquire cocaine self-administration in approximately half the time of non-defeated rats (Haney et al., 1995; Tidey and Miczek, 1997). The results of these studies suggest that certain types of stress can enhance the addictive properties of drugs like cocaine and amphetamine, possibly by enhancing the sensitivity of the mesocorticolimbic dopaminergic system to these substances. Conversely, drug-induced sensitisation of the mesocorticolimbic dopamine system may underlie increased responsiveness to stress.

7. Concluding remarks

Stress sensitisation induced in animals by brief, intense stressful events can yield a syndrome that includes behavioural and physiological disturbances mimicking key-symptoms of anxiety and other affective disorders. There are now several animal models available in the literature for which reported data indicate construct validity and face validity, and occasionally, some predictive validity, for PTSD in particular. In these models, stressors are used that differ in various aspects, e.g. in modality, intensity and frequency. Yet, their most striking, long-lasting behavioural effects show considerable overlap, suggesting a large degree of non-specificity in the underlying mechanisms and substrates. The occurrence of mutual cross-sensitisation induced by stress and psychoactive drugs strengthens this notion.

There are, however, also differences in aspects of the observed long term syndromes between the various animal models. Although it is unknown to date how these differences are brought about, several possible explanations should be considered. One important factor in this respect likely is the intensity of the stress experience. For inescapable footshocks, it has been shown that the long term syndrome induced is crucially dependent, both in quantitative and qualitative terms, on factors as current intensity, shock frequency, and duration and number of stress sessions (Murison and Overmier, 1998). For stressors of other modalities such data are beginning to emerge (Zelena et al., 1999). Another factor that likely contributes heterogeneity in the sensitisation syndromes in animal studies is that stressful stimuli may also induce long lasting changes in (brain) substrates that specifically relate to their modal-

ity. These substrates evidently differ for painful, social or psychological stimuli, and changes induced therein may or may not become expressed depending on the type and timing of the challenge used. The type of challenge used indeed appears to be of considerable importance for sensitisation to be expressed. This is for instance clearly indicated by our data that sensitisation of gut motility responses in preshocked rats is invariably evidenced in a shock prod test executed under low-arousal conditions (in the home cage, when the rats are resting), but behavioural sensitisation is not. Conversely, behavioural sensitisation is invariably expressed when the rats are transferred to a novel environment, but increased general arousal then precludes detection of gut sensitisation (Stam et al., 1996). These observations clearly indicate that, at least for behavioural and autonomic responses, the mechanisms involved in the expression of sensitisation are not identical. They also suggest that differences in the challenges used might be a factor that contributes to the differences between sensitisation syndromes that have been reported. Finally, one should keep in mind that both induction and expression of stress sensitisation are the result of interactions between subject and environment. There exists an extensive literature on the relevance of genetic and ontogenetic factors for varying stress responsiveness. Thus, species and strains of animals, and even individual animals of the same strain can markedly differ in this respect.

Clearly, our understanding of the process of stress sensitisation is far from complete. Future research should aim at careful dissection of the development in time of behavioural, neuro-endocrine and autonomic aspects of sensitisation syndromes, and of individual vulnerability factors for sensitisation. This is of great importance when we keep in mind that PTSD, like other stress associated psychiatric and psychosomatic disorders, anxiety and affective disorders are syndromes that present with a considerable heterogeneity of symptoms between individual patients.

References

Adamec, R., 1997. Transmitter systems involved in neural plasticity underlying increased anxiety and defense — implications for understanding anxiety following traumatic stress. Neurosci. Biobehav. Rev. 21, 755–766.

Adamec, R.E., Shallow, T., 1993. Lasting effects on rodent anxiety of a single exposure to a cat. Physiol. Behav. 54, 101–109.

Adamec, R.E., Burton, P., Shallow, T., Budgell, J., 1999. Unilateral block of NMDA receptors in the amygdala prevents predator stress-induced lasting increases in anxiety-like behavior and unconditioned startle — effective hemisphere depends on the behavior. Physiol. Behav. 65, 739–751.

Antelman, S.M., Eichler, A.J., Black, C.A., Kocan, D., 1980. Interchangeability of stress and am phetamine in sensitization. Science 207, 329–331.

Antelman, S.M., Caggiula, A.R., Kocan, D., Knopf, S., Meyer, D., Edwards, D.J., Barry III, H., 1991. One experience with 'lower' or 'higher' intensity stressors, respectively enhances or diminishes responsiveness to haloperidol weeks later: implications for understanding drug variability. Brain Res. 566, 276–283.

Antelman, S.M., Caggiula, A.R., Gershon, S., Edwards, D.J., Austin, M.C., Kiss, S., Kocan, D., 1997. Stressor induced oscillation: a possible model of the bidirectional symptoms in PTSD. Ann. N.Y. Acad. Sci. 821, 296.

Bartanusz, V., Aubry, J.M., Jezova, D., Baffi, J., Kiss, J.Z., 1993. Up-regulation of vasopressin mRNA in paraventricular hypophysiotrophic neurons after acute immobilization stress. Neuroendocrinology 58, 625–629.

Beckam, J.C., Crawford, A.L., Kirby, A.C., Hertzberg, M.A., Davidson, J.R., Moore, S.D., 1997. Chronic postraumatic stress disorder and chronic pain in Vietnam combat veterans. J. Psychosom. Res. 43, 379–389.

Blaker, D.G., West, S.A., Orth, D.N., Hill, K.K., Nicholson, W.E., Ekhator, N.N., Bruce, A.B., Wortman, M.D., Keck, P.E., Geracioti, T.D., 1997. Cerebrospinal fluid and plasma β-endorphin in combat veterans with post-traumatic stress disorder. Psychoneuroendocrinology 22, 517–529.

Boscarino, J.A., 1997. Diseases among men 20 years after exposure to severe stress: implications for clinical research and medical care. Psychosom. Med. 59, 605–614.

Boscarino, J.A., Chang, J., 1999. Higher abnormal leukocyte and lymphocyte counts 20 years after exposure to severe stress: research and clinical implications. Psychosom. Med. 61, 378–386.

Bremner, J.D., Randall, P., Scott, T.M., Bronen, R.A., Seibyl, J.P., Southwick, S.M., Delaney, R.C., McCarthy, G., Charney, D.S., Innis, R.B., 1995. MRI-based measurement of hippocampal volume in patients with combat-related posstraumatic stress disorder. Am. J. Psychiatry 152, 973–981.

Bremner, J.D., Innis, R.B., Ng, C.K., Staib, L.H., Salomon, R.M., Bronen, R.A., Duncan, J., Southwick, S.M., Krystal, J.H., Rich, D., Zubal, G., Dey, H., Soufer, R., Charney, D.S., 1997a. Positron emission tomography measurement of cerebral metabolic correlates of yohimbine administration in combat-related posttraumatic stress disorder. Arch. Gen. Psychiatry 54, 246–254.

Bremner, J.D., Licinio, J., Darnell, A., Krystal, J.H., Owens, M.J., Southwick, S.M., Nemeroff, C.B., Charney, D.S., 1997b. Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. Am. J. Psychiatry 154, 624–629.

Bremner, J.D., Staib, L.H., Kaloupek, D., Southwick, S.M., Soufer, R., Charney, D.S., 1999. Neural correlates of exposure to traumatic pictures and sound in vietnam combat veterans with and without posttraumatic stress disorder: a positron emission tomography study. Biol. Psychiatry 45, 806–816.

Breslau, N., Kessler, R.C., Chilcoat, H.D., Schultz, L.R., Davis, G.C., Andreski, P., 1998. Trauma and posttraumatic stress disorder in the community. Arch. Gen. Psychiatry 55, 626–632.

Breslau, N., Chilcoat, H.D., Kessler, R.C., Davis, G.C., 1999. Previous exposure to trauma and PTSD effects on subsequent trauma: results from the Detroit area survey of trauma. Am. J. Psychiatry 156, 902–907.

Bruijnzeel, A.W., Stam, R., Compaan, J.C., Croiset, G., Akkermans, L.M., Olivier, B., Wiegant, V.M., 1999a. Long-term sensitization of Fos-responsivity in the rat central nervous system after a single stressful experience. Brain Res. 819, 15–22.

Bruijnzeel, A.W., Stam, R., Croiset, G., Wiegant, V.M., 1999b. Long-term sensitisation of cardiovascular responses to novel challenges after a single stressful experience. Fund. Clin. Pharmacol. 13, 127.

Buwalda, B., De Boer, S.F., Schmidt, E.D., Felszeghy, K., Nyakas, C., Sgoifo, A., Van der Vegt, B.J., Tilders, F.J., Bohus, B., Koolhaas, J.M., 1999. Long-lasting deficient dexamethasone suppression of hypothalamic–pituitary–adrenocortical activation following peripheral CRF challenge in socially defeated rats. J. Neuroendocrinol. 11, 513–520.

Cador, M., Cole, B.J., Koob, G.F., Stinus, L., Le Moal, M., 1993. Central

administration of corticotropin-releasing factor induces long-term sensitization to D-amphetamine. Brain Res. 606, 181–186.

Campeau, S., Watson, S.J., 1997. Neuroendocrine and behavioral responses and brain pattern of c-fos induction associated with audiogenic stress. J. Neuroendocrinol. 9, 577–588.

Casada, J.H., Amdur, R., Larsen, R., Liberzon, I., 1999. Psychophysiologic responsivity in posttraumatic stress disorder: generalized hyperresponsiveness versus trauma specificity. Biol. Psychiatry 44, 1037–1044.

Charney, D.S., Deutch, A., 1996. A functional neuroanatomy of anxiety and fear: implications for the pathophysiology and treatment of anxiety disorders. Crit. Rev. Neurobiol. 10, 419–446.

De Kloet, E.R., Joëls, M., 1999. Stress and cognition: are corticosteroids good or bad guys? Trends Neurosci. 22, 422–426.

De Wied, D., Croiset, G., 1991. Stress modulation of learning and memory processes. Methods Achiev. Exp. Pathol. 15, 167–199.

Diagnostic and Statistical Manual for the Mental Disorders (DSM-IV). American Psychiatric Association, Washington, DC.

Diaz-Otanez, C.S., Del Rosario Capriles, N., Cancela, L.M., 1997. D1 and D2 dopamine and opiate receptors are involved in restraint stress-induced sensitization to the psychostimulant effects of amphetamine. Pharmacol. Biochem. Behav. 58, 9–14.

Foote, S.L., Bloom, F.E., Aston-Jones, G., 1983. Nucleus locus coeruleus: new evidence of anatomical and physiological specifity. Physiol. Rev. 68, 844–914.

Freeman, T.W., Cardwell, D., Karson, C.N., Komoroski, R.A., 1998. In vivo proton magnetic resonance spectroscopy of the medial temporal lobes of subjects with combat-related posttraumatic stress disorder. Magn. Reson. Med. 40, 66–71.

Friedman, M.J., Yehuda, R., 1995. Post-traumatic stress disorder and comorbidity. In: Friedman, M.J., Charney, D.S., Deutch, A.Y. (Eds.), Neurobiological and Clinical Consequences of Stress. Lipincott-Raven, Philadelphia, PA, pp. 429–445.

Gresch, P.J., Sved, A.F., Zigmond, M.J., Finlay, J.M., 1994. Stress-induced sensitization of dopamine and norepinephrine efflux in medial prefrontal cortex of the rat. J. Neurochem. 63, 575–583.

Hamamura, T., Ichimaru, Y., Fibiger, H.C., 1997. Amphetamine sensitization enhances regional c-fos expression produced by conditioned fear. Neuroscience 76, 1097–1103.

Haney, M., Maccari, S., Le Moal, M., Simon, H., Piazza, P.V., 1995. Social stress increases the acquisition of cocaine self-administration in male and female rats. Brain Res. 698, 46–52.

Harper, D.G., Tornatzky, W., 1996. Stress induced disorganization of circadian and ultradian rhythms: comparison of effects of surgery and social stress. Physiol. Behav. 59, 409–419.

Huether, G., 1996. The central adaptation syndrome: psychosocial stress as a trigger for adaptive modification of brain structure and brain function. Prog. Neurobiol. 48, 569–612.

Irwin, C., Falsetti, S.A., Lydiard, R.B., Ballenger, J.C., Brock, C.D., Brener, W., 1996. Comorbidity of posttraumatic stress disorder and irritable bowel syndrome. J. Clin. Psychiatry 57, 576–578.

Kellner, M., Wiedemann, K., Yassouridis, A., Levengood, R., Guo, L.S., Holsboer, F., Yehuda, R., 2000. Behavioral and endocrine response to cholecystokinin tetrapeptide in patients with posttraumatic stress disorder. Biol. Psychiatry 47, 107–111.

Kolta, M.G., Shreve, P., DeSouza, V., Uretsky, N.Y., 2000. Time course of the development of the enhanced behavioral and biochemical responses to amphetamine after pretreatment with amphetamine. Neuropharmacology 24 (9), 823–829.

Koolhaas, J.M., Hermann, P.M., Kemperman, C., Bohus, B., Van den Hoofdakker, R.H., Beersma, D.G.M., 1990. Single social defeat in male rats induces a gradual but long lasting behavioural change: a model of depression? Neurosci. Res. Commun. 7, 35–41.

Kovacs, K.J., 1998. Functional neuroanatomy of the parvocellular vasopressinergic system: transcriptional responses to stress and glucocorticoid feedback. Prog. Brain Res. 119, 31–40.

Kuzmin, A., Semenova, S., Zvartau, E.E., Van Ree, J.M., 1996. Enhancement of morphine self-administration in drug naive, inbred strains of mice by acute emotional stress. Eur. Neuropsychopharmacol. 6 (1), 63–68.

Levine, S., Madden, J.I., 1973. Psychological and behavioral effects of prior aversive stimulation. Physiol. Behav. 10, 467–471.

Liberzon, I., Taylor, S.F., Amdur, R., Jung, T.D., Chamberlain, K.R., Minoshima, S., Koeppe, R.A., Fig, L.M., 1999. Brain activation in PTSD in response to trauma-related stimuli. Biol. Psychiatry 45, 817–826.

Lucey, J.V., Costa, D.C., Adshead, G., Deahl, M., Busatto, G., Gavinovic, S., Travis, M., Pilowsky, L., Ell, P.J., Marks, I.M., Kerwin, R.W., 1997. Brain blood flow in anxiety disorders. Br. J. Psychiatry 171, 346–350.

Ma, X.M., Levy, A., Lightman, S.L., 1997. Rapid changes in heteronuclear RNA for corticotrophin-releasing hormone and arginine vasopressin in response to acute stress. J. Endocrinol. 152, 81–89.

Magos, L., 1969. Persistence of the effect of amphetamine on stereotyped activity in rats. Eur. J. Pharmacol. 6, 200–201.

Maier, S.F., Coon, D.J., McDaniel, M.A., Jackson, R.L., Grau, J., 1979. The time course of learned helplessness, inactivity, and nociceptive deficits in rats. Learn. Motiv. 10, 467–487.

Mason, J.W., Mougey, E.H., 1972. Thyroid (plasma BEI) response to chair restraint in the monkey. Psychosom. Med. 34, 441–448.

Mason, J.W., Wang, S., Yehuda, R., Bremner, J.D., Riney, S., Lubin, H., Johnson, D.R., Southwick, S.M., Charney, D.S., 1995. Some approaches to the study of the clinical implications of thyroid alterations in post-traumatic stress disorder. In: Friedman, M.J., Charney, D.S., Deutch, A.Y. (Eds.), Neurobiological and Clinical Consequences of Stress. Lippincott Raven, Philadelphia, PA, pp. 367–379.

Meerlo, P., De Boer, S.F., Koolhaas, J.M., Daan, S., Van den Hoofdakker, R.H., 1996. Changes in daily rhythms of body temperature and activity after a single social defeat in rats. Physiol. Behav. 59, 735–739.

Meerlo, P., Van den Hoofdakker, R.H., Koolhaas, J.M., Daan, S., 1997. Stress-induced changes in circadian rhythms of body temperature and activity in rats are not caused by pacemaker changes. J. Biol. Rhythms 12, 80–92.

Meerlo, P., Sgoifo, A., De Boer, S.F., Koolhaas, J.M., 1999. Long-lasting consequences of a social conflict in rats: behavior during the interaction predicts subsequent changes in daily rhythms of heart rate, temperature, and activity. Behav. Neurosci. 113, 1283–1290.

Miczek, K.A., 1991. Tolerance to the analgesic, but not discriminative stimulus effects of morphine after brief social defeat in rats. Psychopharmacology 104, 181–186.

Morgan, J.I., Curran, T., 1995. Immediate-early genes: ten years on. Trends Neurosci. 18, 66–67.

Morgan, C.A., Grillon, C., Southwick, S.M., Davis, M., Charney, D.S., 1996. Exaggerated acoustic startle reflex in Gulf War veterans with posttraumatic stress disorder. Am. J. Psychiatry 153, 64–68.

Morgan, C.A., Grillon, C., Lubin, H., Southwick, S.M., 1997. Startle reflex abnormalities in women with sexual assault-related posttraumatic stress disorder. Am. J. Psychiatry 154, 1076–1080.

Murison, R., Overmier, J.B., 1998. Comparison of different animal models of stress reveals a non-monotonic effect. Stress 2, 227–230.

Nisenbaum, L.K., Zigmond, M.J., Sved, A.F., Abercrombie, E.D., 1991. Prior exposure to chronic stress results in enhanced synthesis and release of hippocampal norepinephrine in response to a novel stressor. J. Neurosci. 11, 1478–1484.

Orr, S.P., Meyerhoff, J.L., Edwards, J.V., Pitman, R.K., 1998. Heart rate and blood pressure resting levels and responses to generic stressors in Vietnam veterans with posttraumatic stress disorder. J. Trauma Stress 11, 155–164.

Piazza, P.V., Le Moal, M., 1997. Glucocorticoids as a biological substrate of reward: physiological and pathophysiological implications. Brain Res. Rev. 25, 359–372.

Pitman, R.K., Van der Kolk, B.A., Orr, S.P., Greenberg, M.S., 1990. Naloxone-reversible analgesic response to combat-related stimuli in post-traumatic stress disorder. Arch. Gen. Psychiatry 47, 541–544.

Ramsey, N.F., Van Ree, J.M., 1993. Emotional but not physical stress enhances intravenous cocaine self-administration in drug-naive rats. Brain Res. 608, 216–222.

Rasmusson, A.M., Hauger, R.L., Morgan, C.A., Bremner, J.D., Charney, D.S., Southwick, S.M., 2000. Low baseline and yohimbine-stimulated plasma neuropeptide Y levels in combat-related PTSD. Biol. Psychiatry 47, 526–539.

Ruis, M.A.W., Te Brake, J.H.A., Buwalda, B., De Boer, S.F., Meerlo, P., Korte, S.M., Blokhuis, H.J., Koolhaas, J.M., 1999. Housing familiar male wildtype rats together reduces the long-term adverse behavioural and physiological effects of social defeat. Psychoneuroendocrinology 24, 285–300.

Schmidt, E.D., Janszen, A.W., Wouterlood, F.G., Tilders, F.J., 1995. Interleukin-1-induced long-lasting changes in hypothalamic corticotropin-releasing hormone (CRH)–neurons and hyperresponsiveness of the hypothalamus–pituitary–adrenal axis. J. Neurosci. 15, 7417–7426.

Schmidt, E.D., Binnekade, R., Janszen, A.W.J.W., Tilders, F.J.H., 1996. Short stressor induced long-lasting increases of vasopressin stores in hypothalamic corticotropin-releasing hormone (CRH) neurons in adult rats. J. Neuroendocrinol. 8, 703–712.

Schmidt, E.D., Tilders, F.J., Binnekade, R., Schoffelmeer, A.N., De Vries, T.J., 1999. Stressor- or drug-induced sensitization of the corticosterone response is not critically involved in the long-term expression of behavioural sensitization to amphetamine. Neuroscience 92, 343–352.

Semple, W.E., Goyer, P.F., McCormick, R., Compton-Toth, B., Morris, E., Donovan, B., Muswick, G., Nelson, D., Garnett, M.L., Sharkoff, J., Leisure, G., Miraldi, F., Schulz, S.C., 1996. Attention and regional cerebral blood flow in posttraumatic stress disorder patients with substance abuse histories. Psychiatry Res. 67, 17–28.

Servatius, R.J., Ottenweller, J.E., Bergen, M.T., Soldan, S., Natelson, B.H., 1994. Persistent stress-induced sensitization of adrenocortical and startle responses. Physiol. Behav. 56, 945–954.

Solomon, S.D., Davidson, J.R.T., 1997. Trauma: prevalence, impairment, service use and cost. J. Clin. Psychiatry 58 (Suppl. 9), 5–11.

Sorg, B.A., Kalivas, P.W., 1991. Effects of cocaine and footshock stress on extracellular dopamine levels in the ventral striatum. Brain Res. 559, 29–36.

Sorg, B.A., Kalivas, P.W., 1995. Stress and neuronal sensitization. In: Friedman, M.J., Charney, D.S., Deutch, A.Y. (Eds.), Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to PTSD. Lipincott-Raven, Philadelphia, PA, pp. 83–102.

Southwick, S.M., Yehuda, R., Morgan, C.A., 1995. Clinical studies of neurotransmitter alterations in post-traumatic stress disorder. In: Friedman, M.J., Charney, D.S., Deutch, A.Y. (Eds.), Neurobiological and Clinical Consequences of Stress. Lipincott-Raven, Philadelphia, PA, pp. 335–349.

Southwick, S.M., Krystal, J.H., Bremner, J.D., Morgan, C.A., Nicolaou, A.L., Nagy, L.M., Johnson, D.R., Heninger, G.R., Charney, D.S., 1997. Noradrenergic and serotonergic function in posttraumatic stress disorder. Arch. Gen. Psychiatry 54, 749–758.

Stam, R., Croiset, G., Akkermans, L.M.A., Wiegant, V.M., 1996. Sensitization of the colonic response to novel stress after previous stressful experience. Am. J. Physiol. 271, R1270–R1273.

Stam, R., Akkermans, L.M.A., Wiegant, V.M., 1997. Trauma and the gut: interactions between stressful experience and intestinal function. Gut 40, 704–709.

Stam, R., Croiset, G., Bruijnzeel, A.W., Visser, T.J., Akkermans, L.M.A., Wiegant, V.M., 1999. Sex differences in long-term stress-induced colonic behavioural and hormonal disturbances. Life Sci. 65, 2837–2849.

Stein, M.B., Koverola, C., Hanna, C., Torchia, M.G., McClarty, B., 1997a. Hippocampal volume in women victimized by childhood sexal abuse. Psychol. Med. 27, 951–959.

Stein, M.B., Yehuda, R., Koverola, C., Hanna, C., 1997b. Enhanced dexamethasone suppression of plasma cortisol in adult women traumatized by childhood sexual abuse. Biol. Psychiatry 42, 680–686.

Tidey, J.W., Miczek, K.A., 1997. Acquisition of cocaine self-administration after social stress: role of accumbens dopamine. Psychopharmacology (Berl) 130, 203–212.

Tornatzky, W., Miczek, K.A., 1993. Long-term impairment of autonomic circadian rhythms after brief intermittent social stress. Physiol. Behav. 53, 983–993.

True, W.R., Rice, J., Eisen, S.A., Heath, A.C., Goldberg, J., Lyons, M.J., Nowak, J., 1995. A twin study of genetic and environmental contributions to liability for posttraumatic stress symptoms. Arch. Gen. Psychiatry 50, 257–264.

Van den Berg, C.L., Lamberts, R.R., Wolterink, G., Wiegant, V.M., Van Ree, J.M., 1998. Emotional and footshock stimuli induce differential long-lasting behavioural effects in rats. Brain Res. 799, 6–15.

Vanderschuren, L.J., Schmidt, E.D., De Vries, T.J., Van Moorsel, C.A., Tilders, F.J., Schoffelmeer, A.N., 1999. A single exposure to amphetamine is sufficient to induce long-term behavioral, neuroendocrine, and neurochemical sensitization in rats. J. Neurosci. 19, 9579–9586.

Van Dijken, H.H., Van der Heyden, J.A.M., Mos, J., Tilders, F.J.H., 1992a. Inescapable footshocks induce progressive and long lasting-behavioural changes in male rats. Physiol. Behav. 51, 787–794.

Van Dijken, H.H., Mos, J., Van der Heyden, J.A.M., Tilders, F.J.H., 1992b. Characterization of stress-induced long-term behavioural changes in rats: evidence in favor of anxiety. Physiol. Behav. 52, 945–951.

Van Dijken, H.H., Tilders, F.J.H., Olivier, B., Mos, J., 1992c. Effect of anxiolytic and antidepressant drugs on long-lasting behavioural deficits resulting from one short stress experience in male rats. Psychopharmacology 109, 395–402.

Van Dijken, H.H., De Goeij, D.C.E., Sutanto, W., Mos, J., De Kloet, E.R., Tilders, F.J.H., 1993. Short inescapable stress produces long-lasting changes in the brain-pituitary-adrenal axis of adult male rats. Neuroendocrinology 58, 57–64.

Wang, S., Mason, J., Charney, D., Yehuda, R., Riney, S., Southwick, S., 1997. Relationships between hormonal profile and novelty seeking in combat-related posttraumatic stress disorder. Biol. Psychiatry 41, 145–151.

Watson, C.G., Davenport, E., Anderson, P.E.D., Mendez, C.M.M., Gearhart, L.P., 1998. The relationships between premilitary school record data and risk for posttraumatic stress disorder among Vietnam war veterans. J. Nerv. Ment. Dis. 186, 338–344.

Weyers, P., Bower, D.B., Vogel, W.H., 1989. Relationships of plasma catecholamines to open-field behaviour after inescapable shock. Neuropsychobiology 22, 108–116.

White, F.J., 1996. Synaptic regulation of mesocorticolimbic dopamine neurons. Annu. Rev. Neurosci. 19, 405–436.

Wickelgren, I., 1997. Marijuana: harder than thought? Science 276, 1967–1968.

Yehuda, R., Antelman, S.M., 1993. Criteria for rationally evaluating animal models for posttraumatic stress disorder. Biol. Psychiatry 33, 479–486.

Yehuda, R., Teicher, M.H., Trestman, R.L., Levengood, R.A., Siever, L.J., 1996. Cortisol regulation in posttraumatic stress disorder and major depression: a chronobiological analysis. Biol. Psychiatry 40, 79–88.

Yoshida, K., Morimoto, A., Makisumi, T., Murakami, N., 1993. Cardiovascular, thermal and behavioral sensitization to methamphetamine in freely moving rats. J. Pharmacol. Exp. Ther. 267, 1538–1543.

Zelena, D., Halasz, J., Makara, G.B., 1999. Social stress of variable intensity: physiological and behavioral consequences. Brain Res. Bull. 48, 297–302.