International Journal of Applied Research 2022; 8(6): 604-608

ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 8.4
IJAR 2022; 8(6): 604-608
www.allresearchjournal.com
Received: 04-05-2022
Accepted: 07-06-2022

Dr. Amit Anand
Assistant Professor, Guest Faculty, Department of Chemistry, GD College, Begusarai, Bihar, India

Corresponding Author:
Dr. Amit Anand
Assistant Professor, Guest Faculty, Department of Chemistry, GD College, Begusarai, Bihar, India

A review on stress, drug's uses and vulnerability to addiction

Dr. Amit Anand

Abstract
Stress is a well-known risk factor in the development of addiction and in addiction relapse vulnerability. A series of population-based and epidemiological studies have identified specific stressors and individual-level variables that are predictive of substance use and abuse. Preclinical research also shows that stress exposure enhances drug self-administration and reinstates drug seeking in drug-experienced animals. The deleterious effects of early life stress, child maltreatment, and accumulated adversity on alterations in the corticotropin releasing factor and hypothalamic-pituitary-adrenal axis (CRF/HPA), the extra hypothalamic CRF, the autonomic arousal, and the central noradrenergic systems are also presented. The effects of these alterations on the corticostriatal-limbic motivational, learning, and adaptation systems that include mesolimbic dopamine, glutamate, and gamma-amino-butyric acid (GABA) pathways are discussed as the underlying pathophysiology associated with stress-related risk of addiction. The effects of regular and chronic drug use on alterations in these stress and motivational systems are also reviewed, with specific attention to the impact of these adaptations on stress regulation, impulse control, and perpetuation of compulsive drug seeking and relapse susceptibility. Finally, research gaps in furthering our understanding of the association between stress and addiction are presented, with the hope that addressing these unanswered questions will significantly influence new prevention and treatment strategies to address vulnerability to addiction.

Keywords: Chronic stress, early life stress, addiction risk, relapse, craving, mesolimbic dopamine

Introduction
Stress has long been known to increase vulnerability to addiction. The last decade has led to a dramatic increase in understanding the underlying mechanisms for this association. Behavioral and neurobiological correlates are being identified, and some evidence of molecular and cellular changes associated with chronic stress and addiction has been identified. Human studies have benefited from the emergence of sophisticated brain-imaging tools and the cross examination of laboratory-induced methods of stress and craving and their association to specific brain regions associated with reward and addiction risk. This paper focuses primarily on the association between stress and addiction in humans but also draws from the broader animal literature to support the proposed hypotheses. A definition of stress and its neural underpinnings is presented with specific emphasis on its effects on motivation and behavior. In the context of strong epidemiological evidence linking early-childhood and adult adversity and risk of addiction, results from basic and human research that point to putative mechanisms underlying this association are presented. A critical role is seen for prefrontal circuits involved in adaptive learning and executive function, including controlling distress and desires/impulses, in the association between stress and addiction risk. However, several questions remain unanswered in understanding stress-related addiction risk, and these are reviewed in order to inform future research. Finally, the effects of chronic drug use on stress and reward pathways particularly with respect to relapse risk are examined. Future directions in addressing stress-related relapse risk in clinical settings are also discussed.

Stress, Emotions and Adaptive Behaviours
The term "stress" refers to processes involving perception, appraisal, and response to harmful, threatening, or challenging events or stimuli [1].

Stress experiences can be emotionally or physiologically challenging and activate stress responses and adaptive processes to regain homeostasis [2]. Examples of emotional stressors include interpersonal conflict, loss of relationship, death of a close family member, and loss of a child. Common physiological stressors are hunger or food deprivation, sleep deprivation or insomnia, extreme hyper- or hypothermia, and drug withdrawal states. In addition, regular and binge use of many psychoactive drugs serve as pharmacological stressors. This kind of conceptualization allows the separate consideration of

1. Internal and external events or stimuli that exert demands or load on the organism,
2. The neural processes that evaluate the demands and assess availability of adaptive resources to cope with the demands (appraisal),
3. The subjective, behavioral, and physiological activity that signal stress to the organism,
4. Neuroadaptations in emotional and motivational brain systems associated with chronic stress and
5. Behavioural, cognitive, and physiological adaptation in response to stressors.

While stress is often associated with negative affect and distress, it can include "good stress" which is based on external and internal stimuli that are mild/moderately challenging but limited in duration and results in cognitive and behavioral responses that generate a sense of mastery and accomplishment, and can be perceived as pleasant and exciting [3]. Such situations rely on adequate motivational and executive functioning to achieve goal-directed outcomes and homeostasis [4]. However, the more prolonged, repeated, or chronic the stress-for example, states associated with increased intensity or persistence of distress-the greater the uncontrollability and unpredictability of the stressful situation, lower the sense of mastery or adaptability, and greater the magnitude of the stress response and risk for persistent homeostatic dysregulation [5]. Thus, the dimensions of intensity, controllability, predictability, mastery, and adaptability are important in understanding the role of stress in increasing risk of maladaptive behaviors such as addiction.

The perception and appraisal of stress relies on specific aspects of the presenting external or internal stimuli, personality traits, availability of internal resources (including physiological condition of the individual), prior emotional state (including beliefs and expectancies), and specific brain regions mediating the appraisal of stimuli as distressing, and the resulting physiological, behavioral, and emotional experiences and adaptive responses. Brain regions such as the amygdala, hippocampus, insula, and orbitofrontal, medial prefrontal, and cingulate cortices are involved in the perception and appraisal of emotional and stressful stimuli, and the brain stem (locus ceruleus and related arousal regions), hypothalamus, thalamus, striatal, and limbic regions are involved in physiological and emotional responses. Together these regions contribute to the experience of distress. Physiological responses are manifested through the two major stress pathways, namely corticotropin releasing factor (CRF) released from the paraventricular nucleus (PVN) of the hypothalamus, which stimulates adrenocorticotrophic hormone from the anterior pituitary, which subsequently stimulates the secretion of cortisol/corticosterone from the adrenal glands, and the autonomic nervous system, which is coordinated via the sympathoadrenal medulary (SAM) systems [6].

In addition, CRF has extensive influence in extra hypothalamic regions across the corticostriatal-limbic regions and plays a critical role in modulating subjective and behavioral stress responses [7]. Furthermore, central catecholamines, particularly noradrenaline and dopamine, are involved in modulating brain motivational pathways (including the ventral tegmental area or VTA, nucleus accumbens [NAc], and the medial prefrontal [mPFC] regions) that are important in regulating distress, exerting cognitive and behavioral control, and negotiating behavioral and cognitive responses critical for adaptation and homeostasis [8]. The hypothalamic and extra hypothalamic CRF pathways and central catechoamines target brain motivational pathways to critically affect adaptive and homeostatic processes. For example, different parts of the medial prefrontal cortex are involved in higher cognitive or executive control functions, such as controlling and inhibiting impulses, regulating distress, focusing and shifting attention, monitoring behavior, linking behaviors and consequences over time, considering alternatives before acting, and decision-making responses [9]. Psychosocial and behavioral scientists have elegantly shown that with increasing levels of emotional and physiological stress or negative effect, there is a decrease in behavioral control and increases in impulsivity, and with increasing levels of distress, and chronicity of stress, greater the risk of maladaptive behaviors [10]. Neurobiological evidence shows that with increasing levels of stress, there is a decrease in prefrontal functioning and increased limbic-striatal level responding, which perpetuates low behavioral and cognitive control [11]. Thus, the motivational brain pathways are key targets of brain stress chemicals and provide an important potential mechanism by which stress affects addiction vulnerability.

Stress and development of addictive behaviours

There is a substantial literature on the significant association between acute and chronic stress and the motivation to abuse addictive substances. Many of the major theories of addiction also identify an important role of stress in addiction processes. These range from psychological models of addiction that view drug use and abuse as a coping strategy to deal with stress, to reduce tension, to self-medicate, and to decrease withdrawal-related distress [12], to neurobiological models that propose incentive sensitization and stress allostasis concepts to explain how neuroadaptations in reward, learning, and stress pathways may enhance craving, loss of control, and compulsion, the key components in the transition from casual use of substances to the inability to stop chronic use despite adverse consequences, a key feature of addiction [13]. In this section, we review the converging lines of evidence that point to the critical role that stress plays in increasing addiction vulnerability.

Chronic Adversity and Increased Vulnerability to Drug Use

There is considerable evidence from population-based and clinical studies supporting a positive association between psychosocial adversity, negative effect, and chronic distress and addiction vulnerability. The evidence in this area can be categorized into three broad types. The first includes prospective studies demonstrating that adolescents facing high recent negative life events show increased levels of

drug use and abuse [14]. Negative life events such as loss of parent, parental divorce and conflict, low parental support, physical violence and abuse, emotional abuse and neglect, isolation and deviant affiliation, and single-parent family structure have all been associated with increased risk of substance abuse.

The second type of evidence is the association between trauma and maltreatment, negative affect, chronic distress, and risk of substance abuse. Overwhelming evidence exists for an increased association between childhood sexual and physical abuse and victimization and increased drug use and abuse [15]. There is also some evidence that recent negative life events and physical and sexual abuse each exert somewhat independent risk on addiction vulnerability [16]. In addition to sexual and physical abuse, negative affect and chronic distress states are predictive of addiction vulnerability. Findings indicate that negative affect, including temperamental negative emotionality, is associated with substance abuse risk [17]. Several studies have also shown a significant association between prevalence of mood and anxiety disorders, including post-traumatic stress disorder (PTSD), behavioral conduct problems and increased risk of substance use disorders [18]. As stress is significantly associated with prevalence of mood and anxiety disorders and chronic psychiatric distress [19], these associations raise the issue of whether psychiatric disorders conceptualized as chronic distress states may largely account for the significant association between stress and substance use disorders.

In the third type of evidence from population studies, recent research has examined lifetime exposure to stressors and the impact of cumulative adversity on addiction vulnerability after accounting for a number of control factors such as race/ethnicity, gender, socioeconomic status, prior drug abuse, prevalence of psychiatric disorders, family history of substance use, and behavioral and conduct problems [20]. Cumulative adversity or stress was assessed using a checklist method and by counting the number of different events that were experienced in a given period during the lifespan. The effects of distal (events occurring more than 1 year prior) and proximal stress experiences (events during the most recent 1-year period), and their effects on meeting criteria for substance use disorders were also assessed. The findings indicate that the cumulative number of stressful events was significantly predictive of alcohol and drug dependence in a dose-dependent manner, even after accounting for control factors. Both distal and proximal events significantly and independently affected addiction vulnerability. Furthermore, the dose-dependent effects of cumulative stressors on risk for addiction existed for both genders and for Caucasian, African-American, and Hispanic race/ethnic groups. The types of adverse events significantly associated with addiction vulnerability were parental divorce or conflict, abandonment, forced to live apart from parents, loss of child by death or removal, unfaithfulness of significant other, loss of home to natural disaster, death of a close one, emotional abuse or neglect, sexual abuse, rape, physical abuse by parent, caretaker, family member, spouse, or significant other, victim of gun shooting or other violent acts, and observing violent victimization. These represent highly stressful and emotionally distressing events, which are typically uncontrollable and unpredictable in nature.

Stress exposure increases initiation and escalation of drug self-administration

There is some evidence from animal studies to support the notion that acute exposure to stress increases initiation and escalation of drug use and abuse. For example, in animal models, social defeat stress, social isolation, tailpinch and foot-shock, restraint stress, and novelty stress are known to enhance acquisition of opiates, alcohol, and psychostimulant self-administration, with caveats relating to stressor type, genetic background of animals, and variations by drug type. Also, although there are some negative findings, other evidence indicates that early life stress, using procedures such as neonatal isolation or maternal separation, and prolonged and repeated stressors representing chronic stress experiences, enhances self-administration of nicotine, psychostimulants, and alcohol and/or their acute behavioral effects [21]. Notably, sex plays an important role in stress-related sensitivity to the reinforcing effects of drugs and in stress enhancement of drug self-administration [22]. In humans, there is substantial evidence from prospective and longitudinal studies to support the effects of stress on drug use initiation and escalation in adolescents and young adults [23]. Furthermore, there are sex differences in the effects of early trauma and maltreatment on the increased risk of addiction [24]. Laboratory studies examining effects of stress exposure on drug use are limited to legal drugs such as alcohol and nicotine, for ethical reasons. Nonetheless, there is evidence that stress increases drinking and nicotine smoking, but the effects of drinking history, history of adversity, social stress, and expectancies are known to play a role in these experimental studies.

Possible mechanisms underlying stress effects on addiction vulnerability

As evidence using diverse approaches has accumulated in support of a significant effect of stress on risk of addiction, this section examines research on neurobiological links between stress and reward pathways activated by abusive drugs. It is well known that the reinforcing properties of drugs of abuse involve their activation of the mesolimbic dopaminergic (DA) pathways, which include dopamine neurons originating in the ventral tegmental area and extending to the ventral striatum and the prefrontal cortex (PFC) [25]. This pathway is also involved in assigning salience to stimuli, in reward processing, and in learning and adaptation [26]. Human brain imaging studies also support the role of these systems in drug reward, as psychostimulants, alcohol, opioids, and nicotine all activate the mesolimbic DA systems, in particular, the ventral and dorsal striatum, and such activity has been associated with the drug ratings of high or euphoria and craving [27].

However, stress exposure and increased levels of glucocorticoids (GC) also enhance dopamine release in the NAc [28]. Suppression of GC by adrenalectomy reduces extracellular levels of dopamine under basal conditions and in responses to stress and psychostimulants [29]. However, chronic GC inhibits DA synthesis and turnover in the NAc [30], suggesting that alterations in the hypothalamic-pituitary-adrenal (HPA) axis and glucocorticoids can significantly affect DA transmission. There is also evidence that, like drugs of abuse, stress and concomitant increases in CRF and glucocorticoids enhance glutamate activity in the VTA, which in turn enhances activity of dopaminergic neurons [31]. Human brain imaging studies have further shown that stress-

related increases in cortisol are associated with dopamine accumulation in the ventral striatum [32], and some evidence also reveals that amphetamine-induced increases in cortisol are associated with both dopamine binding in the ventral striatum and with ratings of amphetamine-induced euphoria [33]. Given that both stress and drugs of abuse activate the mesolimbic pathways, it is not surprising that each results in synaptic adaptations in VTA dopamine neurons and in morphological changes in the medial prefrontal cortex [34].

In addition to a role in reward, a growing body of human imaging studies and preclinical data indicate that the ventral striatum is also involved in aversive conditioning, in experience of aversive, pain stimuli, and in anticipation of aversive stimuli. Such evidence points to a role for the mesolimbic dopamine pathways beyond reward processing, and one that more broadly involves motivation and attention to behavioral response during salient (aversive or appetitive) events. Furthermore, additional regions connected to the mesolimbic DA pathways and involved in reward, learning, and adaptive and goal-directed behaviors are the amygdala, hippocampus, insula, and related corticolimbic regions. These regions, along with the mesolimbic DA pathways, play an important role in interoception, emotions and stress processing, impulse control and decision making, and in the addictive properties of drugs of abuse.

References

1. Lazarus RS. Stress and Emotion: A New Synthesis. Springer Publishing Company. New York; c1999.
2. Cohen S, Kessler RC, Gordon LU. Strategies for measuring stress in studies of psychiatric and physical disorders. In: Cohen S, Kessler RC, Gordon LU, editors. Measuring Stress: A Guide for Health and Social Scientists. Oxford University Press; New York; c1995. p. 3-26.
3. Levine S. Developmental determinants of sensitivity and resistance to stress. Psych Neuroendocrinology. 2005;30:939-946.
4. Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. Annu. Rev. Physiol. 2005;67:259-284.
5. McEwen BS. Protective and damaging effects of stress mediators: The good and bad sides of the response to stress. Metabolism. 2002;51:2-4.
6. McEwen BS. Physiology and neurobiology of stress and adaptation: Central role of the brain. Physiol. Rev. 2007;87:873-904.
7. Selye H. The Stress of Life. McGraw-Hill; New York; c1976.
8. Paulus MP. Decision-making dysfunctions in psychiatry–altered homeostatic processing? Science. 2007;318:602-606.
9. Frankenhauser M. Psychobiological aspects of life stress. In: Levine S, Ursin H, editors. Coping and Health. Plenum Press; New York: c1980. p. 203-223.
10. Lovallo WR. Stress & Health: Biological and Psychological Interactions. Sage Publications, Inc.; Thousand Oaks, CA; c1997.
11. Meaney MJ, Brake W, Gratton A. Environment regulation of the development of mesolimbic dopamine systems: A neurobiological mechanism for vulnerability to drug abuse? Psych Neuroendocrinology. 2002;27:127-138.
12. McEwen BS. Stress and hippocampal plasticity. Annu. Rev. Neuro-Sci. 1999;22:105-122.
13. Heinrichs S. Behavioral consequences of altered corticotropin-releasing factor activation in brian: a functionalist view of affective neuroscience. In: Steckler T, Kalin NH, Reul JMHM, editors. Handbook of Stress and the Brain. Part 1: The Neurobiology of Stress. Elsevier; Amsterdam. 2005;15:155-177.
14. Berridge CW. Noradrenergic modulation of arousal. Brain Res. Rev. 2007;58(1):1-17.
15. Phan KL *et al*. Neural substrates for voluntary suppression of negative affect: A functional magnetic resonance imaging study Biol. Psychiatry. 2005;57:210-219.
16. Roberts A, Robbins T, Weiskrantz L. The Prefrontal Cortex: Executive and Cognitive Functions. Oxford University Press; Oxford, UK; c1998.
17. Arnsten AFT. The biology of being frazzled. Science. 1998;280:1711-1712.
18. Mischel W. From Good Intentions to Willpower. Guilford Press; New York; c1996.
19. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. Psychol. Bull. 1997;121:65-94.
20. Tice D, Bratslavsky E, Baumeister R. Emotional distress regulation takes precedence over impulse control: If you feel bad, do it! J. Pers. Soc. Psychol. 2001;80:53-67.
21. Westergaard GC, *et al*. Physiological correlates of aggression and impulsivity in free-ranging female primates. Neuropsychopharmacology. 2003;28:1045-1055.
22. Hayaki J *et al*. Adversity among drug users: relationship to impulsivity. Drug Alcohol Depend. 2005;78:65-71.
23. Greco B, Carli M. Reduced attention and increased impulsivity in mice lacking NPY Y2 receptors: relation to anxiolytic-like phenotype. Behav. Brain Res. 2006;169:325-334.
24. Fishbein DH *et al*. Mediators of the stress-substance-use relationship in urban male adolescents. Prev. Sci. 2006;7:113-126.
25. Verdejo-Garcia A *et al*. Negative emotion-driven impulsivity predicts substance dependence problems. Drug Alcohol Depend. 2007;91:213-219.
26. Anestis MD, Selby EA, Joiner TE. The role of urgency in maladaptive behaviors. Behav. Res. Ther. 2007;45:3018-3029.
27. Hatzinger M *et al*. Hypothalamic-pituitary-adrenocortical (HPA) activity in kindergarten children: importance of gender and associations with behavioral/ emotional difficulties. J. Psychiatr. Res. 2007;41:861-870.
28. Arnsten AFT, Goldman-Rakic PS. Noise stress impairs prefrontal cortical cognitive function in monkeys: Evidence for a hyperdopaminergic mechanism. Arch. Gen. Psychiatry. 1998;55:362-369.
29. Li CS, Sinha R. Inhibitory control and emotional stress regulation: Neuroimaging evidence for frontal-limbic dysfunction in psycho-stimulant addiction. Neurosci. Biobehav. Rev. 2008;32:581-597.
30. Sinha R. How does stress increase risk of drug abuse and relapse? Psychopharmacology (Berl.). 2001;158:343-359.

31. Tomkins SS. Psychological model of smoking behavior. Am. J. Public Health & the Nation's Health. 1966;56:17-20.
32. Leventhal H, Cleary PD. The smoking problem: A review of the research and theory in behavioral risk modification. Psychol. Bull. 1980;88:370-405.
33. Russell JA, Mehrabian A. The mediating role of emotions in alcohol use. J. Stud. Alcohol. 1975;36:1508-1536.
34. Marlatt GA, Gordon JR. Relapse Prevention: Maintenance Strategies in the Treatment of Addictive Behaviors. Guilford Press; New York; c1985.