ISSN: 2641-6271
DOI: 10.33552/OAJAP.2020.04.000579
Open Access Journal of Addiction and Psychology
Iris Publishers

Short Communication

Incorporating Neurocircuitry in Relapse Prevention

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Received Date: July 25, 2020

Published Date: August 17, 2020

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To the extent that drug addiction is recognized as a relapsing condition, it seems curious that standard approaches aimed at treating addictive disorders do not include addressing the brain circuitry adaptations that define the disorder itself. Even as the transition to addiction is said to involve neuroplasticity in multiple brain centers that participate in 'binge/intoxication', 'withdrawal/negative affect' and 'preoccupation/anticipation' (or craving), scant attention seems to be placed on mediating the neurobiological components underlying the stress systems involved in addiction [1]. One is left wondering why incorporating stress modification approaches wouldn't assist in the restoration of fundamentally dysregulated neurochemical mechanisms that make up chronic drug dependence and the vulnerability to relapse [2].

While the California Department of Healthcare Services (DHCS) has adopted medication assisted treatment (MAT) as its principle means of combatting the opioid overuse epidemic, this approach primarily consists of counseling and behavioral therapy, coupled with the administration of buprenorphine, naltrexone and the FDA-approved narcotic methadone.

In that recognized neurobiological changes in substance abuse disorders include a compromised reward system, overactivated stress circuits and dependence-induced reward dysregulation [3], it may be ambitious to imagine that by themselves counseling and therapy might provide enough of a neurological impact to reconfigure dysregulated brain systems involved in stress related relapse. That's where appropriately applied stress management strategies can be used effectively.

When administered strategically, biofeedback has encountered reasonable levels of success in moderating stress-related transduction factors specific to the transmission of pain, one of the principle applications of the long-term use of opioids [4]. These treatment effects have remained stable and have proved to be robust across different methods of effect size calculation [5]. My own experience spanning 13 years of hospital-based chronic pain involvement has demonstrated that individuals who entered our program addicted to opioids and benzodiazapines could safely titrate off of narcotics entirely and learn to manage and reduce their pain levels at the same time [6].

The degree to which these results have endured may provide a glimpse into the expansive and multi-faceted role that stress assumes in both pain signal conduction and mu-opioid tolerance. The number of brain circuitry operations affected by stress is extensive, and includes various mechanisms at the cellular, neuronal and neurotransmitter levels.

One example is the neural basis of drug craving, where 'liking' and 'wanting' drugs persists even after long periods of abstinence. The psychological/neurobiological basis of craving seems to involve the ability to attribute 'incentive salience' to enhanced mesotelencephalic dopamine transmission [7]. Incentive salience refers to a psychological process that imbues the perception of an event with salience, making the operant stimuli appear wanted, attractive and incentivized. For many individuals, the subsequent repeated administration of addictive drugs has the effect of producing incremental neuroadaptations in the dopamine system,

making it increasingly hypersensitive to continuing drug-associated episodes (i.e. sensitized).

Another example of the influence stress systems have on opioid tolerance involves the physical interactions between mu opioid and alpha 2A adrenergic receptors. These G-protein coupled receptor complexes reside in close proximity in living cells, and colocalize in proximal dendrites in primary hippocampal neurons [8]. Research has determined that activation of either mu or alpha 2A adrenergic receptors results in a significant increase in the level of G-protein activated signaling [9]. Since the opioid-adrenergic cross-talk affects the nociceptive pain signaling system, this coupled interaction appears to represent something of a blueprint for the development of opioid-induced hyperalgesia.

Similarly, the cross-regulation between mu opioid receptor (MOR) and glutamate ionotropic receptor N (GluN) also plays a significant role in the modulation and transmission of the nociceptive signals involved in the analgesic efficacy of morphine, and this association is diminished following the activation of GluN receptors [10]. Research indicates that in the nervous system, the functional interaction of opioids with G protein coupled MOR initiates the development of analgesic tolerance and physical dependence, with a number of signaling proteins having been identified. These include nitric oxide synthase (NOS), protein kinase A (PKA), calcium (Ca2+)/calmodulin (CaM)-dependent kinase II and the regulators of G-protein signaling (RGS) proteins, which are supported by the functional association between MORs and the N-methyl-D-aspartate acid glutamate receptor (NMDAR) [11].

As it turns out, chronic opioid exposure produces a range of nervous system-based adaptations related to compulsive use and relapse, including MOR tolerance, cellular withdrawal and tolerance in opioid-sensitive neurons, and withdrawal and tolerance in opioid-sensitive nerve networks. These neuroadaptations additionally encompass synaptic plasticity in neuropeptide systems that interact with mu-opioid sensitive neurons and extend to synaptic forms of learning including long term potentiation (LTP) and longterm depression (LTD) [12].

MOR-related activation is associated with drug reward and dependence in the amygdala, a brain center associated with drug craving and relapse [13]. While the synaptic activity in the amygdala is linked with chronic stress and excitatory glutamatergic transmission, the glutamatergic signaling is associated with anxiety and depression [14]. These alterations in glutamate transmission are believed to represent a significant factor contributing to drug addiction [15].

Amygdala noradrenaline is associated with drug dependence and regarded as a primary influence on emotional states that drive drug-seeking, through the dysregulation of emotional systems that mediate stress and arousal. As a result, activated stress circuitry is hypothesized to be a principle component underlying the pathophysiology of addiction [16].

Research indicates this to be the case at multiple levels, including cellular, molecular and neurotransmission [17]. Stress responses are said to compromise executive functioning in three stages: at the binge/intoxication stage, the withdrawal/negative affect stage and the preoccupation/anticipation stage [18]. Stress plays a role in the development of opioid tolerance, drug dependency and relapse; and addiction is said to specifically encompass the involvement of the autonomic nervous system [19], which has demonstrated amenability for targeted regulation in a variety of stress-related health concerns over the past 50 years [20].

Perhaps the time has come to incorporate dysregulated circuitry adjustment into standard substance abuse disorder treatment protocols.

Acknowledgement

None.

Conflict of Interest

Author declare no conflict of interest.

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