Addiction: A Literature Review of Biological Factors Leading to Addictive Tendencies and Potential Treatments

Gabriel Mandel, BS

Sackler School of Medicine, Tel Aviv University, Tel Aviv

Abstract

Addiction is an epidemic; the consequences of an addiction can tear apart families and cause immeasurable damage to many lives. Based on medical literature from the past twenty years, this paper focuses on common biological changes present in addiction and medical treatments available and being researched. Specifically, critical changes observed in the levels of dopamine receptors, transcription factors, and stress hormones, are analyzed. In addition, by assessing the treatments, including vaccines that block the entry of substances through the blood brain barrier and surgical interventions that act directly on the area of the brain that controls addiction, the biological changes are better understood. Overall, this paper provides a review of past research and medical breakthroughs in the field of addiction, as well as the burgeoning directions in this field.

Micah Belzberg: *Prescription*

Introduction

Addiction is characterized by a loss of control, or a dramatic behavioral change "from impulsivity to compulsivity" (1). Behaviors, which had once been engaging for pleasure, become painfully forced and addicts are unable to cease their behavior. Substance dependence specifically is defined by the American Psychiatric Association as "a maladaptive pattern of substance use that subsequently leads to clinical impairment or distress" (2). It is diagnosed by the appearance of specific symptoms when three or more occur within 12 months. These symptoms include, but are not limited to, increased substance tolerance, withdrawal, increased intake, recurrent desire to reduce substance use, frequent drug-seeking behaviors, reduction in social, occupational or recreational activities, and continual substance use despite deleterious physical or psychological consequences (2). Or as summarized by Dr. George Koob in three major symptoms: "compulsion to seek, loss of control in limiting intake, negative emotional state with withdrawal" (1). Signals that the addict associates with addiction (such as friends, locations, drug equipment) can remind him of his previous behaviors and thereby cause a relapse. Like substance addictions, non-drug addictions appear in similar psychological and behavioral patterns including craving, impaired control over the behavior, tolerance, withdrawal, and high rates of relapse (3).

The modelling of addiction as a brain disease is controversial, as is the equation of behavioral abuses with addiction (4-6). In spite of this, this paper attempts to present some of the ongoing research into changes that the brain undergoes under pathological activity. Although every substance and behavior that is abused has a variety of different effects on the brain, this paper will attempt to focus on the common factors seen in behavioral abuses and substance abuses.

Materials and Methods

A Google Scholar search was performed using keywords, such as: addiction, compulsion, behavioral addiction, biology of addiction, neurobiology of addiction, ablative surgery, and deep brain stimulation.

Results

Biological Basis of Addiction

Associated Brain Regions

The reward regions of the brain seem to have evolved long ago. The basis for the complex reward pathways present in mammals has existed for nearly 2 billion years, when flies and worms evolved. They evolved to regulate a creature's responses to natural rewards, like food, sex, and social interaction, and are therefore critical for survival. The areas implicated in addiction are grouped together and referred to as the mesocorticolimbic projection. This consists of dopaminergic neurons in the ventral tegmental area (VTA) of the midbrain and their targets in the limbic forebrain, especially the nucleus accumbens (NAc), and the prefrontal cortex. Every drug of abuse regardless of its distinct method of action converges on this pathway with common acute effects. Several other brain areas that network with the VTA and NAc are essential for the chronic changes associated with addiction. Specific portions of the limbic system (namely, the amygdala, hippocampus, and hypothalamus) are associated with addiction. The amygdala is important to help to assess whether an experience is pleasurable or aversive and whether it should be repeated or avoided and to create connections between an experience and associated cues. The hypothalamus is crucial for the stress activation system. The hippocampus functions to record the memories of an experience. Additionally, the cingulum, which allows for communication between areas of the limbic system, is a central structure in learning to correct mistakes. These regions are the traditional areas of memory formation and their association implies that addiction involves emotional memory (7). The orbitofrontal cortex, a sub-region of the prefrontal cortex, contributes to the impulsivity and compulsivity that characterizes an addicted state (8).

Key Point: Dopaminergic Areas and Associated Pathways in the Brain

Ventral tegmental area of midbrain:

- Mesocortical pathway: Blockage leads to increased negative symptoms of schizophrenia
- Mesolimbic pathway: Blockage relieves positive symptoms of schizophrenia

Substantia nigra pars compacta of midbrain:

- Nigrostriatal pathway: Damage may lead to Parkinson's disease

Arcuate nucleus of hypothalamus:

- Tuberoinfundibular pathway: Blockage leads to increased prolactin release

Fitzgerald, P., & Dinan, T. G. (2008). Prolactin and dopamine: What is the connection? A review article. J Psychopharmacol, 22(2 suppl), 12–19.

Nestler E. J., Hyman S. E., & Malenka, R. C. (2009). Molecular Neuropharmacology: A Foundation for Clinical Neuroscience, 2nd Ed., McGraw-Hill, New York.

Plasticity

Every cell contains some 20,000 to 25,000 protein-coding genes; cells differ from each other based on which of these genes are expressed. Cells retain

the capability to change which specific genes are expressed to adapt to changes. In the nervous system this capacity is especially important because neurons do not generally undergo mitosis. Therefore, the changes in the brain, including newly created synapses and extended dendrites, are the method in which the nervous system adapts to external stimuli. The repeated stimulation, caused by drugs of abuse and abusing natural rewards, repeatedly activates the body's natural reward system and creates changes in the brain not seen through natural activation of this system. By consistently activating this system, these drugs and behaviors change the nerve cells in the reward pathways. The cells change in terms of the neurotransmitters released, and consequently morphological changes occur. These changes severely affect a person and in some extreme cases addicts cannot respond normally to natural rewards, and instead depend on drug and their addictive behaviors for the sense of reward. The effects of addiction are long lasting and addicts remain susceptible to relapse long after they have ceased their behavior. This implies that a dramatic, lasting change has occurred in their neuro-circuitry caused by changes in gene expression.

Receptors

Receptor Activation

Dopamine is the primary neurotransmitter involved in the reward pathway. It is released in response to all natural rewards. There are two families of dopamine receptors on postsynaptic neurons, D1 type receptors and D2 type receptors. The D1 family includes D1 and D5 receptors; the D2 family includes D2, D3 and D4 receptors. The D1 family consists of two G-protein coupled receptors (GPCR) and when activated, they stimulate adenylate cyclase to convert adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP) within the cell. The D2 family receptors consist of three GCPRs and when activated they stimulate Gi alpha to inhibit ATP from being converted to cAMP. When induced, cAMP activates cAMP-dependent protein kinase A (PKA) which subsequently activates transcription factors that allow genes to be read and produce mRNA and eventually be translated to protein.

D2 Receptor Levels

It appears that in a brain in an addicted state there are a lower proportion of D2 receptors expressed in the cell membrane. Low levels of dopamine D2 receptors have been seen in individuals addicted to cocaine, alcohol, opiates, as well as in people with obesity. This is true to the extent that in obese individuals the D2 receptor levels were inversely correlated with their BMI. It is possible that the decrements in dopamine D2 receptors in obese individuals represent a down regulation to compensate for dopamine increases caused by chronic dopamine release. It is also possible that individuals that previously expressed low numbers of D2 receptors may be more vulnerable to addiction (9).

Transcription Factors

Transcription factors are proteins that control gene expression. Transcription factors are essential proteins in the process of addiction.

CREB

An important transcription factor implicated in addiction is the cAMP response-element binding protein (CREB). It leads to the production of many proteins associated with addiction and appears to promote tolerance. Overexpression of CREB in the NAc inhibits the rewarding effects of drugs of abuse and natural rewards. One protein that CREB upregulates, dynorphin, inhibits the activity of dopamine cells and reduces the release of dopamine from presynaptic neurons. This reduces the sense of reward produced by drugs and natural rewards, thereby promoting tolerance (10).

ΔFosB

The transcription factor ΔFosB is a common pathway for addictive tendencies. The family of Fos transcription factors heterodimerize with the family of Jun proteins. The heterodimers form activator protein-1 (AP-1) complexes, causing gene expression or repression. Most Fos family proteins are induced after acute exposure to drugs and natural rewards; the spliced ΔFosB however accumulates after chronic exposure (7). This is due to its very stable structure (8). The high molecular stability of ΔFosB means it

is retained in neurons for several weeks after abusive behaviors have ceased, before returning to normal levels. However, the behavioral changes caused by these addictions may reoccur years after ceasing these behaviors. Therefore, ΔFosB must affect other molecules in order to cause the long-term behavioral effects. Consequently, it seems as though ΔFosB acts as a "molecular switch" which begins the genesis of addiction (11).

Overexpression of ΔFosB increases behavioral responses to drugs and natural rewards. Silencing ΔFosB's transcription activity reduced behavioral responses to drugs of abuse and natural rewards. Conversely, when ΔFosB is expressed even without drug use or natural reward stimulation, then the behaviors and changes associated with addiction do occur. This implies that ΔFosB is both necessary and sufficient for the behavioral features associated with addiction (8). Interestingly, when cocaine is self-administered it induces several times more ΔFosB than when it is researcher-administered. This volitional aspect of addiction implicates the prefrontal cortex (which controls conscious decision-making) in addiction pathogenesis (12).

Downstream Proteins Induced by ΔFosB (Table 1)

ΔFosB also increases the sense of reward. It increases the expression of glutamate receptor 2 (GluR2), an AMPA glutamate receptor subunit that significantly reduces the conductivity of AMPA receptors and makes the channel impermeable to Ca2+. This has been seen to increase the rewarding effects of cocaine (7).

ΔFosB increases the expression of cyclin dependent kinase 5 (Cdk5), a protein kinase required for neuronal development, survival and synaptic signaling. It has been directly linked to increases in dendritic spine density. Another protein upregulated by ΔFosB is nuclear factor kappa B (NF-κB). It has previously been implicated in the plasticity of learning and memory, in addiction it has been seen to be necessary for increased dendritic spine density and for the rewarding effects of drug use. Increased dendritic spine density may create new neural connections that solidify a behavioral propensity towards reward (8).

ΔFosB may also cause an increase in brain derived neurotrophic factor (BDNF). BDNF, a growth factor, increases the neuronal dendritic density in the NAc and the prefrontal cortex. Animals chronically exposed to stimulants (such as cocaine) show increased levels of BDNF in VTA of the brain, and exogenous BDNF causes animals to act as if they are dependent on drugs. On the other hand, mice that did not express BDNF (through a gene knockout) display less drug seeking behavior (13).

Table 1. Proteins induced by ΔFosB and their effects.

Upregulated Protein	Neural effects	Behavioral effects
GluR2	Reduces AMPA conductivity	Increased drug reward
Cdk5	Increased dendritic density	Addictive tendencies
NF-κB	Increased dendritic density	Increased drug reward Addictive tendencies
BDNF	Increased dendritic density	Addictive tendencies

Stress and Addiction

Corticotropin releasing factor (CRF) is recognized to play a key role in relapse. CRF is a 41 amino acid polypeptide present throughout the brain with particularly high concentrations in the amygdala. CRF increases the levels of adrenocorticotropic hormone, which, in turn, increases cortisol levels. Cortisol has global effects in the body and stimulates the fight or flight response. This pathway is activated during withdrawal from all drugs of abuse. Competitive CRF receptor antagonists have been found to reduce stress as well as drug seeking behavior (1).

Environmental Enrichment and Exercise

Enriched environments (EE) containing novel objects, exercise equipment and social partners, provides reinforcement to animals; it is shown to activate the mesolimbic dopaminergic system. Significant neural plasticity is observed when animals are housed in an enriched environment. This includes

drastic changes in brain weight, angiogenesis, neurogenesis, gliogenesis, and dendritic structure in response to environmental enrichment. The plasticity caused by EE appears to reduce the sensitivity to drugs of abuse and seems to cause a "protective phenotype" against drug use. For example, following psychostimulant treatment, EE caused reduced sensitivity to nicotine, as well as reduced cocaine self-administration and drug-seeking behavior. EE did not lead to differences in NAc dopamine synthesis in the mesolimbic projection; in the prefrontal cortex, EE reduced dopamine transport capacity. Due to the connection between the prefrontal cortex and the mesolimbic projection, this could impact mesolimbic activity, impulsivity, and consequently drug self-administration. EE significantly reduced the activity of CREB and reduced BDNF in the NAc following 30 days EE. This "protective" effect is so significant that it has potential for protecting and improving recovery from neurological diseases including schizophrenia, Huntington's and Parkinson's diseases (3).

Treatments

Vaccines

A critical mechanism of substance addiction is the capability of the substance to reach the brain, the target of its effects. If the substance can be prevented from crossing the blood-brain-barrier, then the addictive effects of the substance will be eliminated. To this end, vaccines for morphine, nicotine, methamphetamine, and cocaine have been developed. It is most effective to prevent relapse in cocaine users who are motivated to cease their use, since enough cocaine will overwhelm the antibodies produced by the vaccine. The theory is that the vaccine may be able to prevent limited use from turning into a full-scale binge and complete relapse (14-15). However, this therapy seems to be of little use, as many addictions cause a cross-sensitization, i.e. an addiction to one substance can easily lead to abusing another substance, and therefore immunity to one substance will not solve the problem (16).

Stereotactic Neurosurgical Treatments

Ablative stereotactic neurosurgery creates small lesions in the central nervous system, in order to change a particular form of neural activity. Areas in the frontal cortex, hypothalamus, anterior cingulum, cingulate gyri, and NAc have been targeted with varying success rates. These procedures have been mostly terminated for reasons regarding their efficacy, safety, and ethical implications.

Deep Brain Stimulation (DBS) is a particularly successful treatment for many disorders. It has proven to be helpful for a variety of neurological conditions such as Parkinson's disease, chronic pain, depression, Tourette syndrome and obsessive compulsive disorder. Although it has some possible serious side effects, they are generally reversible. In DBS, electrical current is applied to areas of the brain through stereotactically implanted electrodes; high-frequency stimulation at similar targets as the ablative surgeries produces clinical effects similar to ablation, but unlike ablation, DBS effects are generally reversible once the stimulation ceases (17). Research studies have tested DBS for alcohol, cocaine, opioid, tobacco, binge eating, morphine, and heroin abuse. The most promising region for implantation is the NAc. The mechanism of DBS is unknown, but one hypothesis is that it normalizes the firing of neurons and thereby eventually rectifies the changes due to addiction (18). As of yet, there have been no double-blind studies published on DBS' efficacy for addiction.

Medication

Some medications function by blocking the effects of drugs. One example of this method is naltrexone. Naltrexone is effective in treating alcohol, nicotine and behavioral addictions. It blocks the receptors in the brain for endorphins and opiates, and thereby blocks opiates' capacity to amplify dopamine release (19). That is to say, if rewarding behaviors are no longer rewarding, because naltrexone is blocking the sense of reward, then addiction can be ameliorated. Morning use of naltrexone blocks the euphoria that accompanies the behaviors and substances, and thereby makes drug relapse less likely. Over time, this treatment may cease the association these behaviors with positive reinforcement. However, the clinical use of naltrexone is limited because it is associated with low rates of compliance, apparently due to the fact that naltrexone induces dysphoria (10).

Some substance addictions can be treated with substitution therapy, that is, to stimulate the body in a similar fashion as the substance would. The idea is to provide similar stimulation in a more controlled manner to wean the body off its dependence. For example, an addiction to cigarettes can be treated with nicotine prepared in a safer mechanism of delivery, such as nicotine patches or nicotine chewing gum. For opiate addictions, administration of a long-acting oral, such as levo-α-acetylmethadol (LAAM) or methadone is administered. They have a much shorter half-life; and must be slowly tapered. This treatment suppresses craving and drug-seeking behavior. Similarly, buprenorphine, a partial μ-opioid-receptor agonist, is used. It blocks the effects of heroin by binding to the μ-receptor and only partially activating the receptor. These drugs are usually administered in the context of highly structured psychosocial interventions, as they themselves have potential for abuse and addiction. However, unlike naltrexone, buprenorphine does not produce dysphoria. Suboxone, a combination of buprenorphine and naloxone, is a promising therapy in the long-term treatment of opiate addiction. By smoothing out the highs and lows that often characterize heroin use, this treatment facilitates rehabilitation and increases an individual's ability to sustain employment and stabilize social relationships (17).

Discussion and Future Steps

Dynorphin, mentioned earlier as being stimulated by CREB, produces dysphoria by acting on κ-opioid receptors. This raises the possibility that κ-opioid antagonists may be useful in the treatment of withdrawal; this has been supported by animal models. A goal of current research is to identify other CREB-regulated genes and define their influence on drug tolerance and dependence. CRF, the hormone that induces stress, has been also been a major area of research. CRF antagonists have reversed the negative effects of cocaine, ethanol, and opiate withdrawal in animal models and have reduced drug-seeking behavior (20).

The current pharmacological treatments for addiction either imitate the manner in which drugs activate receptors or they block the drugs action on receptors.

Key Point: Roles of Dopamine Outside of Reward/Addiction pathway

Dopamine produced in the pars compacta promotes movement via activation of the direct excitatory pathway (D1 Receptor)

Dopamine produced in the hypothalamus inhibits prolactin secretion from the anterior pituitary gland

Dopamine works in the prefrontal cortex to promote a tightly regulated working memory

Dopamine works in the frontal lobes to promote cognition

Cools, R. (2008). Role of Dopamine in the Motivational and cognitive control of behavior. The Neuroscientist, 14(4), 381–395.

Wise, R. A. (2004) Dopamine, learning and motivation. Nature Reviews Neuroscience 5, 483-494.

They don't focus on the changes in the brain that determine the addiction process. An appreciation of the changes at the molecular level taking into account all the changes previously discussed can hopefully lead to the development of new types of medications that target these changes.

An interesting possibility that may arise from the studies performed on ΔFosB is the possibility of using ΔFosB as a marker for addiction. Or in the words of Dr. Eric Nestler, ΔFosB can be a "biomarker to assess the state of activation of an individual's reward circuitry, as well as the degree to which an individual is 'addicted', both during the development of an addiction and its gradual waning during extended withdrawal or treatment" (8).

More research is necessary to identify the connection between the manner in which addiction is expressed and the actual biological changes that take place. This research will be very closely related to the research into learning, depression, and stress activation. All of these areas are inextricably intertwined and will all shed light on one another. Many of the same

pathways are affected in all of these conditions, and treatment of one will probably produce possibilities for the others.

This highlights the necessity to have a structured form of healthy living and social sphere. The research into EE indicates that a healthier environment produces important neurological changes that assist in recovering from addiction. Therefore, a primary component of addiction therapy should be psychosocial assistance in the form of cognitive–behavioral interventions, community reinforcement and 12-step facilitation (the various anonymous groups). These rehabilitation methods will help repair and rebuild the addict's life. The medications prescribed and being researched will make rehabilitation more effective by overcoming the neuro-circuitry that became disposed to addiction.

Conclusion

Addiction is a complex disease that poses enormous challenges to healthcare and society. The concomitant processes of learning, memory, and reward complicate and inform this disease. Continuing research that identifies its pathogenesis will lead to better understanding and treatment. Current research has identified key biological markers that are promising targets for the development of drugs.

Acknowledgements

The author wishes to thank Ann Shinnar for her guidance.

References

1. Koob, G. F., & Simon, E. J. (2009). The neurobiology of addiction: Where we have been and where we are going. Journal of Drug Issues, 39(1), 115–132.
2. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.
3. Olsen, C. M. (2011). Natural rewards, neuroplasticity, and non-drug addictions. Neuropharmacology,61(7), 1109–1122.
4. Hall, W., Carter, A., & Forlini, C. (2015). The brain disease model of addiction: Is it supported by the evidence and has it delivered on its promises? The Lancet Psychiatry, 2(1), 105–110.
5. Longo, D. L., Volkow, N. D., Koob, G. F., et al. (2016b). Neurobiologic advances from the brain disease model of addiction. New England Journal of Medicine, 374(4), 363–371.
6. Robbins, T., & Clark, L. (2015). Behavioral addictions. Current Opinion in Neurobiology, 30, 66–72.
7. Nestler, E. J. (2005). Is there a common molecular pathway for addiction? Nature Neuroscience, 8(11), 1445–1449.
8. Nestler, E. J. (2013). ΔFosB: A molecular switch for reward. Journal of Drug and Alcohol Research, 2, 1–11.
9. Wang, G.-J., Volkow, N. D., Logan, J., et al. (2001). Brain dopamine and obesity. The Lancet,357(9253), 354–357.
10. Nestler, E. J., Hyman, S. E., & Malenka, R. C. (2008). Molecular Neuropharmacology: A Foundation for Clinical Neuroscience, Second Edition (2nd ed.). New York: McGraw-Hill Companies, Medical Pub. Division.
11. Ruffle, J. K. (2014). Molecular neurobiology of addiction: What's all the (Δ)FosB about? The American Journal of Drug and Alcohol Abuse, 40(6), 428–437.
12. Nestler, E. J. (2013). Cellular basis of memory for addiction. Dialogues in Clinical Neuroscience, 15(4), 431–443.
13. Vargas-Perez, H., Ting-A-Kee, R., Walton, C. H., et al. (2009). Ventral tegmental area BDNF induces an opiate-dependent-like reward state in naive rats. Science, 324(5935), 1732–1734.
14. Kinsey, B. (2014). Vaccines against drugs of abuse: Where are we now? Therapeutic Advances in Vaccines, 2(4), 106–117.
15. Kosten, T. R., Rosen, M., Bond, J., et al. (2002). Human therapeutic cocaine vaccine: Safety and immunogenicity. Vaccine, 20(7-8), 1196–1204.
16. Shaffer, H. J., LaPlante, D. A., LaBrie, R. A., et al. (2004). Toward a syndrome model of addiction: Multiple expressions, common etiology. Harvard Review of Psychiatry, 12(6), 367–374.
17. Lu, L., Wang, X., & Kosten, T. R. (2009). Stereotactic neurosurgical treatment of drug addiction. The American Journal of Drug and Alcohol Abuse,35(6), 391–393.
18. Luigjes, J., van den Brink, W., Feenstra, M., et al. (2011). Deep brain stimulation in addiction: A review of potential brain targets. Molecular Psychiatry, 17(6), 572–583.
19. Bostwick, J. M., & Bucci, J. A. (2008). Internet sex addiction treated with naltrexone. Mayo Clinic Proceedings, 83(2), 226–230.
20. Carroll, F. I., & Carlezon, W. A. (2013). Development of kappa opioid receptor antagonists. Journal of Medicinal. Chem, 56(6), 2178–2195.