Review Article ISSN 2639-8451

Addiction Research

New Perspective on Addiction: The Hypothesis of Rebound Effect

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Received: 03 October 2021; **Accepted:** 28 October 2021

Citation: Domina Petric. New Perspective on Addiction: The Hypothesis of Rebound Effect. Addict Res. 2021; 5(1): 1-5.

ABSTRACT

Addiction alters the levels of all happy brain hormones. My hypothesis is that addictive stimuli cause high amplitude changes in happy brain hormones with initially very high levels followed by very low levels (rebound effect). On the other hand, non-addictive stimuli such as creative work, moderate physical activity, healthy diet, healthy relationships and socialization, cause moderate amplitude changes in happy brain hormones with stable levels of dopamine, serotonin, endorphins and oxytocin without rebound effect. Therefore, all of these non-addictive stimuli might be very helpful in the treatment of addiction.

Keywords
Addiction, Rebound, Stimuli.

Introduction
Addiction is a brain disorder characterized by compulsive engagement in rewarding stimuli despite adverse consequences. Despite the involvement of a number of psychosocial factors, a biological process, one which is induced by repeated exposure to an addictive stimulus, is the core pathology that drives the development and maintenance of an addiction. The two properties that characterize all addictive stimuli are that they are reinforcing (they increase the likelihood that a person will seek repeated exposure to them) and intrinsically rewarding (they are perceived as being inherently positive, desirable, and pleasurable) [1,2].

Addiction and Happy Brain Hormones
There are four major chemicals in the brain that influence brain happiness: dopamine, oxytocin, serotonin and endorphins.

Endorphin happiness is triggered by physical pain. The body's natural morphine masks pain, which allowed human ancestors to run from predators when injured. Humans experience endorphin as euphoria, but it obviously did not evolve to trigger a constant feeling of joy. Dopamine happiness is triggered in a context of getting a new reward. When an individual sees a finish line, brain releases dopamine. Humans evolved to save dopamine for those moments when an important goal is within reach. Oxytocin happiness is triggered when we trust those around us. It promotes bonding between mother and child, and between sex partners. Humans did not evolve to feel oxytocin happiness all the time because there is no survival value in trusting people who are not trustworthy. Serotonin happiness is triggered when an individual feels important. Animals release serotonin when they dominate a resource. Their serotonin falls when they cede a resource to avoid conflict [3].

Addiction is a disorder of the brain´s reward system which arises through transcriptional and epigenetic mechanisms and develops over time from chronically high levels of exposure to an addictive stimulus (food, cocaine, sexual activity, gambling…). DeltaFosB (ΔFosB), a gene transcription factor, is a critical component and common factor in the development of virtually all forms of behavioral and drug addictions. Two decades of research have demonstrated that addiction arises, and the associated compulsive behavior intensifies or attenuates, along with the overexpression of ΔFosB in the D1-type medium spiny neurons of the nucleus accumbens. ΔFosB expression in these neurons directly and positively regulates drug self-administration and reward sensitization through positive reinforcement, while decreasing sensitivity to aversion [4-7].

Dopamine

The release of dopamine in the nucleus accumbens plays a role in reinforcing qualities of many forms of stimuli, including naturally reinforcing stimuli like palatable food and sex [8,9]. Dopamine is the primary neurotransmitter of the reward system in the brain. It plays a role in regulating movement, emotion, cognition, motivation, and feelings of pleasure. Natural rewards, like eating, as well as recreational drug use cause a release of dopamine, and are associated with the reinforcing nature of these stimuli [10].

Nearly all addictive drugs, directly or indirectly, act upon the brain´s reward system by heightening dopaminergic activity [11]. Excessive intake of many types of addictive drugs results in repeated release of high amounts of dopamine, which in turn affects the reward pathway directly through heightened dopamine receptor activation. Prolonged and abnormally high levels of dopamine in the synaptic cleft can induce receptor downregulation in the neural pathway. Downregulation of mesolimbic dopamine receptors can result in a decrease in the sensitivity to natural reinforcers [10].

Serotonin

Müller and Homberg reviewed the role of the serotonergic (5-HT) system in the establishment of drug use-associated behaviors on the one hand and the transition and maintenance of addiction on the other hand for the drugs: cocaine, amphetamine, methamphetamine, MDMA (ecstasy), morphine/heroin, cannabis, alcohol, and nicotine. Results showed a crucial, but distinct involvement of the 5- HT system in both processes with considerable overlap between psychostimulant and opioidergic drugs and alcohol. Functional model suggests specific adaptations in the 5-HT system, what coincides with the establishment of controlled drug use-associated behaviors. These serotonergic adaptations render the nervous system susceptible to the transition to compulsive drug use behaviors and often overlap with genetic risk factors for addiction [12].

Oxytocin

Oxytocin is known as the hormone of love. Endogenous oxytocin arouses feelings of pleasure, peace and security when in the company of a partner [13].

The release of endogenous oxytocin from the pituitary gland into the bloodstream is triggered by sexual stimuli such as hugging, touching, and genital and nipple stimulation in both males and females, and its plasma level is correlated with the levels of arousal and lubrication, reaching a peak during orgasm [14].

The release of endogenous oxytocin decreases fearfulness and works as an anxiolytic agent, diminishing the level of anxiety through inhibiting fear responses in the amygdala, which contains substantial number of oxytocin receptors [15].

Ecstasy [(3,4-methylenedioxymethamphetamine (MDMA)] is a recreational psychoactive drug and is often called the love pill. Research has shown that ecstasy stimulates endogenous oxytocin activity via activation of serotonin 5-HT1A receptors resulting in an increase in feelings of love, empathy and connection to others [16].

A rise in endogenous oxytocin results in an increase of plasma endorphins, natural pain-killers that can diminish pain in women who suffer dyspareunia, due to anxiety or a lack of trust in their partner during the first stages of their relationship [17,18].

Endorphines

Endorphins are morphine-like chemicals produced by the body that help diminish pain while triggering positive feelings. Sometimes referred to as the brain's feel-good chemicals, endorphins are natural painkillers that are released from the pituitary gland of the brain during exercise, emotional stress or pain. The brain is deeply impacted by the abuse of drugs and alcohol. Tolerance builds when an individual takes more of a substance to obtain the same impact on the body. Neurotransmitters in the brain impact the reward system of the body and the risk of addiction can increase when drugs or alcohol are used to the point of tolerance. Substance abuse impacts two neurotransmitter pathways: dopaminergic and opioidergic systems [19,20].

There is evidence that chronic opiate treatment affects levels, biosynthesis and/or release of endogenous opioid peptides. Thus, prolonged morphine treatment in rats inhibits synthesis of β- endorphin in the neurointermediate pituitary lobe via a mechanism involving a decrease in the activity of mRNA coding for the β-endorphin/ACTH precursor. This treatment, in contrast, increases concentrations of immunoreactive dynorphin - in parallel to vasopressin and oxytocin in this lobe. β-endorphin levels in rat plasma after chronic morphine treatment are reduced in comparison to controls. There is no obvious relationship of these effects to the development of tolerance/dependence, but it seems possible that some protracted effects of opiate intake are related to such changes in endorphin metabolism [21].

VTA Gaba Neurons

Al-Hasani and coworkers published a study, in which they showed, in both male and female mice, that long-range GABAergic projections from the ventral tegmental area (VTA) to the ventral nucleus accumbens (NAc) shell, but not to the dorsal NAc shell or NAc core, are engaged in reward and reinforcement behavior. This GABAergic projection exclusively synapses on to cholinergic interneurons (CINs) in the ventral NAc shell, thereby serving a specialized function in modulating reinforced reward behavior through the inhibition of ventral NAc shell CINs. These findings highlight the diversity in the structural and functional topography of VTA GABAergic projections, and their neuromodulatory interactions across the dorsoventral gradient of the NAc shell [22].

VTA GABA neurons have increasingly been recognized as involved in reward and aversion, as well as potential targets for the treatment of addiction, depression and other stress-linked disorders [23].

Hypothesis

Addictive stimuli cause a more sudden and higher increase in happy brain hormones than non-addictive stimuli do, similar to highly palatable food with high glycemic index that causes sudden and higher increase in glucose than healthy moderately palatable food with low glycemic index does. As in the case of food, after the higher increase in blood glucose levels, hyperinsulinemia occurs with consequent hypoglycemia, addictive stimuli probably cause lower levels of happy brain hormones after the initial burst (rebound effect), in comparison with non- addictive stimuli that probably do not cause high amplitude changes in happy brain hormones. After some time, tolerance develops, what means that an individual, who is suffering from addiction disorder, needs to increase the dose of addictive stimulus and shorten the intervals between two consummations of addictive stimulus. On the other hand, non-addictive stimuli, similar to food with low glycemic index, cause moderate increase of happy brain hormones with slower and longer lasting release of dopamine, serotonin, endorphins, and in the case of relationships and sexual love, oxytocin, just like the glucose levels are moderately increased after ingestion of food with low glycemic index, with no rebound hypoglycemia.

Creative Work

Zabelina and coworkers suggested in their article that their findings support the idea that dopamine levels in multiple brain areas affect human creativity, with an interaction between frontal and striatal dopaminergic pathways [24].

According to Baba Shiv, a marketing professor at Stanford´s Graduate School of Business, creativity resides at the intersection of two primary pathways in the brain: serotonergic and dopaminergic.

The right neurochemical cocktail for the best creative work is a high level of both serotonin and dopamine [25].

Creative work is an example of positive feedback. Engagement in creative work (art, science…) increases the plasticity in dopaminergic and serotonergic pathways, and with further increase in levels of dopamine and serotonin, an individual becomes more competent in creative work. Creative work, especially art, can be used to treat addiction, because it provides stable increase in dopamine and serotonin levels, without rebound effect. Moderate physical exercise, healthy balanced diet, humor, healthy relationships and socialization might also be very helpful in the treatment of addiction.

The Link Between Frustration and Addiction

In psychology, frustration is a common emotional response to opposition, related to anger, annoyance and disappointment. Frustration arises from the perceived resistance to the fulfillment of an individual´s will or goal and is likely to increase when a will or goal is denied or blocked [26,27]. There are two types of frustration: internal and external. Internal frustration may arise from challenges in fulfilling personal goals, desires, instinctual drives and needs, or dealing with perceived deficiencies, such as a lack of confidence or fear of social situations. Conflict, such as when one has competing goals that interfere with one another, can also be an internal source of frustration and can create cognitive dissonance. External causes of frustration involve conditions outside an individual´s control, such as a physical roadblock, a difficult task or the perception of wasting time [28].

There are multiple ways individuals cope with frustration such as passive-aggressive behavior, anger or violence, although frustration may also propel positive processes via enhanced effort and strive [29]. A defense mechanism is an unconscious psychological mechanism that reduces anxiety arising from unacceptable or potentially harmful stimuli [30].

Frustration can also initiate defense mechanisms. Frustration causes cognitive dissonance, which is defined as mental discomfort (psychological stress) experienced by a person who holds two or more contradictory beliefs, ideas, or values. This discomfort is triggered by a situation in which a person´s belief clashes with new evidence perceived by the person. When confronted with facts that contradict beliefs, ideals, and values, people will try to find a way to resolve the contradiction to reduce their discomfort [31,32].

Frustration is usually generated in situations when reality contradicts an individual´s needs, goals, expectations, values, causing cognitive dissonance. In order to achieve cognitive consonance (homeostasis of the mind) defense mechanisms are initiated.

Both Sigmund and Anna Freud studied defense mechanisms, but Anna spent more of her time and research on five main mechanisms, which are all responses to anxiety and how the consciousness and unconscious handle the stress of a social situation [33].

These mechanisms are:
Repression: a feeling is hidden and forced from the consciousness to the unconscious because it is seen as socially unacceptable.
Regression: falling back into an early state of mental/physical development seen as less demanding and safer.
Projection: possessing a feeling that is considered as socially unacceptable and instead of facing it, that feeling or unconscious urge is seen in the actions of other people.
Reaction formation: acting the opposite way that the unconscious instructs a person to behave, often exaggerated and obsessive. **Example:** if a wife is infatuated with a man who is not her husband, reaction formation may cause her to, rather than cheat, become obsessed with showing her husband signs of love and affection.
Sublimation: seen as the most acceptable of the mechanisms, an expression of anxiety in socially acceptable ways.

Frustration very often causes formation of knots of negative emotions and thoughts. Best way to deal with frustration is to find positive emotions and thoughts that bring back the homeostasis of the mind. When one goal is blocked, causing the formation of the mind knots, frustrated individual has to find a new goal that is realizable and find positive thoughts about the new goal. Example: person X is not admitted to faculty A, but is admitted to faculty

B. First goal (to be admitted to faculty A) is blocked and there is frustration caused by contradiction between reality and the goal with the consequent cognitive dissonance. This frustration will probably cause the formation of the mind knots (thoughts about failure and incompetence, emotions such as sadness, anger). If the person X does not find a new goal, negative thoughts and emotions will accumulate and worsen the state of cognitive dissonance. If the person X finds a new goal, therefore sign into the faculty B, and succeeds in this goal, there will be positive thoughts and emotions about this accomplishment (thoughts about success, emotions of joy, happiness). This new situation will help the person X to restore the homeostasis of the mind and to achieve cognitive consonance.

Ambition is a strong wish to achieve something, a strong desire for success, achievement, power, or wealth [34].

Healthy ambition can be defined as healthy wish or desire for success, achievement, power, or wealth based on real competencies, talents, motivation, and it is never contradictory with moral values.

Unhealthy ambition is contradictory with moral values and with real competencies, talents, motivation. Individuals with unhealthy ambition usually do not have what it takes to achieve something, but are obsessed with success. This obsession usually causes falling out of reality with the development of mental constructions, and sometimes, even delusions. Individuals with unhealthy ambition usually believe that the goal justifies the means, whilst individuals with healthy ambition tend not to break moral laws. Unhealthy unfulfilled ambition is a common cause of frustration and it is usually associated with neurotic defense mechanisms.

Frustration, unhealthy ambition and addiction are closely related. Frustration causes cognitive dissonance with low levels of happy brain hormones, what can lead to the development of addiction.

Addiction causes short-term increase in happy brain hormones, especially dopamine, (and in the case of sex addiction and oxytocin), with the development of tolerance, what means that the dose of the addiction has to be increased (for example, dose of the drug) and the intervals between consuming the addiction have to be shorter (consummation of the drug has to be more frequent).

Frustration, unhealthy ambition and addiction close the vicious circle

To save oneself from this vicious circle, it is important to manage frustration with new goals, positive emotions, positive thoughts, and to avoid addiction. Instead of unhealthy unrealistic ambition, it is important to develop healthy realistic ambition based on real competencies, talents and motivation.

Conclusion

Addiction alters the levels of all happy brain hormones. My hypothesis is that addictive stimuli cause high amplitude changes in happy brain hormones with initially very high levels followed by very low levels (rebound effect). After some time, tolerance develops, what means that an individual, who is suffering from addiction disorder, needs to increase the dose of addictive stimulus and shorten the intervals between two consummations of addictive stimulus. On the other hand, non-addictive stimuli such as creative work, moderate physical activity, healthy diet, healthy relationships and socialization, cause moderate amplitude changes in happy brain hormones with stable levels of dopamine, serotonin, endorphins and oxytocin without rebound effect. Therefore, all of these non-addictive stimuli might be very helpful in the treatment of addiction.

In addition to that, VTA GABA neurons seem to have neuromodulatory interactions across the dorsoventral gradient of the NAc shell, what means that this newly discovered reward circuity could be an interesting target for the development of new ″anti-addiction″ drugs. Treatment of addiction disorders is complex and requires a multidisciplinary approach, which includes psychiatrist, psychologist, social worker, specialized nurse, pharmacologist and in some cases, spiritual/theological support (for religious individuals only). It is very important to stop the development of pathological neuronal pathways created by abnormal happy brain hormones chemical profile and induce the creation of new healthy neuronal pathways based on healthy and stable happy brain hormones chemical profile.

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