

The Physiology of the HPA and Extended Amygdala in Mechanisms of Drug

Use and Abuse

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Abstract

BACKGROUND. This paper attempts to explain drug abuse, more specifically alcoholism, in terms of neurophysiology and psychological processes in order to gain a greater understanding of drug/alcohol addiction through stress systems and addiction mechanisms. **METHOD.** This was done by consulting online databases (PUBMED, EBSCO) and relevant textbooks for relevant information. **RESULTS.** It was found that the hypothalamic pituitary adrenal (HPA) axis and the extended amygdala were the major physiological systems associated with stress response and drug addiction. These systems work by promoting hedonic homeostatic dysfunction through psychological mechanisms such as a/b-processes, allostasis, sensitization and counteradaptation. **DISCUSSION.** Other factors that increase the vulnerability of consuming drugs consist of genetic factors and external stress. Future research should focus on genetic factors because of the little knowledge and direct understanding we have of genetic factors contributing to the transition from alcohol use to alcohol abuse. Deeper understanding of genetic factors on drug addiction would provide more effective treatment for those suffering from alcohol dependence.

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Introduction

This paper attempts to explain drug abuse, more specifically alcoholism, in terms of neurophysiology and psychological processes. In order to understand the mechanisms of drug use in this way the underlying physiological systems associated with stress must first be clearly understood; these systems include the “extended” amygdala and the hypothalamic-pituitary-adrenal (HPA) axis. After describing these physiological systems, a review of the mechanisms and theories of alcohol use is provided. In the first section we describe the neurophysiology behind drug addiction. In the second section we describe the overall transition between drug use and abuse. Finally we relate the first two sections to alcohol abuse.

Hypothalamic-Pituitary-Adrenal Axis (HPA) function

The Hypothalamic-Pituitary-Adrenal Axis (HPA) is a main physiological stress system in the human body and has been identified as a contributor in the transition from alcohol use to abuse (Schepis et al., 2011). In order to understand this transition from use to abuse it is important to realize the HPA’s physiological responses and processes that occur during exposure to stress. ¹

Central Nervous System and the Hypothalamus. During exposure to stress the central nervous system (CNS), the cerebral cortex and other brain systems activate a part of the brain called the hypothalamus. The hypothalamus is a well-known part of the brain

¹ Material in the HPA section was primarily taken from a lecture by Igor Mitrovic, MD that was derived from a medical physiology textbook by Boron and Boulpaep.

that releases hormones that control bodily functions such as sex drive, intake of food, body temperature and feelings of stress. These feelings of stress, often called anxiety, originate when Corticotropin-releasing factor (CRF) is released into the bloodstream to activate other areas of the brain; CRF can also act as an analog of stress itself (Rodriguex de Fonseca & Navarro, 1998). When the CNS and the cerebral cortex relay stress signals to the hypothalamus, the hypothalamus releases CRF into the bloodstream through either portal circulation to the pituitary gland or through systematic circulation to distant tissues. It is the interaction between CRF and the pituitary gland that furthers the physiological stress response.

Pituitary Gland. The pituitary gland is then the next step in the process of physiological stress response. The pituitary gland has two parts; the anterior pituitary which produces hormones and the posterior pituitary which contains axon terminals from the hypothalamus that produce neurotransmitters. The pituitary gland communicates with the hypothalamus by these neurotransmitters and a shared blood supply; the inferior hypophyseal artery goes from the hypothalamus to the posterior pituitary gland (the part with axon terminals) and the superior hypophyseal artery goes from the hypothalamus into the anterior (hormone producing) pituitary gland. When CRF enters the pituitary gland, the anterior pituitary produces a hormone called corticotropin (ACTH). Once blood makes it through a stressed person's pituitary gland, it contains high levels of ACTH (and other hormones) that drain out and get circulated into the adrenal gland.

Adrenal Gland. The adrenal gland is the last part of the main HPA system. The adrenal gland is located on top of the kidneys and has two glands associated with it: the adrenal medulla and the adrenal cortex. The adrenal medulla secretes dopamine and other

catecholamines and releases them into the bloodstream. The adrenal cortex secretes steroid hormones; the primary hormone of interest from the adrenal cortex is cortisol, which can last 60-90 minutes in the bloodstream before it reaches the liver to be excreted. Cortisol from the adrenal gland stops production of ACTH from the pituitary gland and CRF from the hypothalamus in a negative feedback mechanism. This homeostatic mechanism exists to stop the HPA stress system from chronic up regulation. The Cortisol and CRF that were already created then affect the extended amygdala, which continues the physiological stress response.

Extended HPA axis/Extended Amygdala function

The CRF from the HPA axis activates CRF mechanisms throughout the body, including in the extended amygdala (Koob & Moal, 2006). This action creates additional stress hormones; the excess of stress hormones can cause additional problems when it comes to drug abuse. To understand these problems the function of the extended amygdala must first be understood.

Amygdala function. The extended amygdala is made up of several brain parts including the hippocampus, the amygdala, the stratum and subcomponents of each (Heimer, 1995). The extended amygdala's stress response starts with the cortex signaling the amygdala of stress exposure through glutamate neurotransmitters. The amygdala has four nuclei: the cortical nucleus, the lateral nucleus, the basal nucleus and the central nucleus (LeDoux, 2007)². The cortical nucleus directly receives olfactory information and for the discussions of this review is not critical. The lateral nucleus receives auditory and other sensory information via the hypothalamus or the cortex. The lateral nucleus then sends its signals to the central nucleus through the basal nucleus or other parts, again

² Material in the section on amygdala function sub-section comes primarily from LeDoux, 2007.

through glutamate neurotransmitters. When the signals arrive at the central nucleus, the signals go into the medial region of the central nucleus (a sub-nucleus of the central nucleus) and then to the brain stem which provokes emotional output such as fear and anxiety. The basal nucleus not only helps send signals from the lateral nucleus to the central nucleus to promote these emotional responses but also sends signals to the striatal areas.

Stratum function. The stratum is responsible for behavioral responses and is a large part of the brain that communicates through GABA neurotransmitters as opposed to the glutamate neurotransmitters seen in the amygdala and cortex communications. In fact, Swanson and Petrovich (1998) ascertained that it was possible to identify areas of the stratum based on their GABAergic properties. The stratum is composed of two major areas: the ventral striatum and the pallidum. The ventral striatum is composed of the ventral tegmental area (VTA) which contains the nucleus accumbens (Boron & Boulpaep, 2002). The VTA is thought to play a role in cognition, motivation, psychiatric disorders and drug addiction through a reward system called the mesocortolimbic dopamine system (Oades & Halliday, 1987); the VTA is where dopaminergic cell bodies originate in order to be used by the mesocortolimbic dopamine system (Hosp et. al, 2011). The VTA's input from the basal nucleus of the amygdala gets converted into motor output through the nucleus accumbens (Hosp et. al, 2011), which is a part of the VTA and contains dense GABAergic neurons. These neurons connect the limbic system to motor function (LeDoux, 2007). These neurons are also considered to be the pleasure center of the brain because dopamine neurotransmitters activate this area to create pleasurable feelings (Sabatinelli, 2007); this pleasure is the reward response that links the

HPA axis to drug use through the drug mechanisms discussed later. GABAergic neurons work by inhibiting their targets; however, their targets were inhibiting other neurons before they were acted upon so that when the targets are inhibited those other neurons can function (Purves et al., 2001). In other words, the targets of the GABAergic neurons fire continuously until the stratum tells them to stop, but since the signals they send are inhibitory when they are inhibited they allow their targets to function. This is considered a double inhibition process; the output of this double inhibition process is an activated pallidum (Purves et al., 2001).

Pallidum function. The pallidum is composed of the globus pallidus and the ventral pallidum (Chakravarthy et al., 2010). These two parts work together receive input from the stratum in order to either promote or inhibit motor function. The signal on whether to promote or inhibit motor function goes to the thalamus and then to the cerebral cortex where muscles are signaled to do what is commanded of them (Stocco et al., 2010). In the case of our stress response, actions may include running away or more long term actions in response to anxiety like fear and stress.

The cohesive extended amygdala. Summarizing the extended amygdala, sensory information from the cortex goes into the lateral nucleus where it is either sent to the basal nucleus to be sent to the stratum (or to be relayed to the central nucleus) or the central nucleus to be sent to the medial region of the central nucleus into the brainstem to provoke emotional response. When signals reach the stratum they go into the VTA which then promotes motor function through the dense neurons of the nucleus accumbens to the pallidum where muscles are signaled via the thalamus and the cortex to perform motor functions. This process makes up the extended amygdala/extra-hypothalamic

system. When the HPA produces cortisol and CRF during stress response, they both go to the extended amygdala. The cortisol promotes behavioral responses through the basal nucleus of the amygdala and the stratum and the CRF produces anxiogenic effects through the central nucleus of the amygdala. CRF also down regulates the euphoria of drug use that we will be talked about next.

Drug use and the mechanisms and theories of drug abuse

Alcohol is a stressor on the human body and therefore activates the stress systems described in the previous sections (Thayer et al., 2006); however, there is now a new aspect of euphoria that is introduced with drug use that was not present during the physiological discussion on stress systems (Rodriguez & Navarro, 1998). The elevated neurotransmitter activity of dopamine is characteristically experienced during alcohol use (Yoshimoto et al., 1992). Dopamine provides feelings of euphoria because it is a pleasure center activator neurotransmitter (Grace, 2000): when it activates dopamine receptors in the brain (especially in the nucleus accumbens), elevated pleasure (euphoria) is experienced. Likewise, when alcohol ‘wears off’ these elevated feelings of pleasure are reduced to levels below what were experienced before alcohol consumption for a period of time (“rebound”) (Koob & Moal, 2006). It is the process of fluctuating levels of pleasure, stress and anxiety that aid in the transition from initial drug use to chronic drug use by the HPA and extended amygdala dysfunction through changing hedonic set points derived from the fluctuations (Koob, 1996). The dysfunction of the HPA and extended amygdala shows itself in several processes throughout drug abuse.

A/B processes. Koob (2003) and others propose that drug/alcohol use has two main stages: an initial stage with elevated levels of pleasure (euphoria) due to elevated

levels of dopamine followed by a stage in which these feelings of pleasure are reduced to levels below the initial baseline level (a negative state). These stages are called a-processes and b-processes, respectively. The level of mood at which the drug user is accustomed to functioning when not using is considered a baseline level of mood--neither positive euphoria nor a negative state is in effect (Koob, 2003). The time spent in each stage of drug use depends on the experience of the user with that drug and unique individual differences between users (McEwen, 1998).

The main physiological system associated with a-process drug/alcohol use states is the mesocortolimbic dopamine system (Chiara, 2003). The mesocortolimbic system is activated during drug use to produce dopamine that, acting upon the nucleus accumbens and extended amygdala, produce euphoria according to Chiara. The euphoria produced by the nucleus accumbens and the extended amygdala can mask stress produced by the extended amygdala (since drugs are stressors) until b-processes begin to predominate; B-process systems include those producing CRF, primarily including the HPA and extended amygdala (Koob & Moal 2006).

During initial drug/alcohol exposure, a-process states predominate followed by a small dip below baseline (b-process) before mood returns to baseline (called the hedonic set point because it is the level at which the body is used to functioning)³. This holds true for the first several encounters with a drug. In fact, sometimes repeated exposure to a drug shows increasing euphoric effects for the user for a short time after drug initiation; this is called “sensitization”. Sensitization can be explained by the formation of more dopamine (D2) receptors in the nucleus accumbens after initiation of a drug (so that

³ Unless otherwise noted, material from this point until the ‘Allostasis’ section was primarily derived from *Neurobiology of Addiction* by Koob and Moal (2006).

dopamine in the same quantities has increasing effects). This may work to trigger instability of the hedonic set point through incentive salience mechanisms ('wanting' mechanisms) because of intense cravings for the drug initially due to increasing pleasurable effects. However tolerance tends to follow after repeated exposure to a drug. Therefore, motivation for initial drug use is the positive reinforcement of euphoria early in the drug/alcohol use cycle where very little side effects are present.

Homeostatic dysregulation. After moderate to extreme drug use the a-process stage gets shorter and is followed by an increasingly larger b-process stage. Drug users experience less and less euphoria (due to higher threshold of activating a-processes) and more and more dysphoria and stress (due to increasingly active b-processes); this, according to Koob and others, marks the transition from drug use to addiction. This signals the transition from drug use to addiction because as the a-process stage gets shorter and the b-process stage gets shorter, the hedonic set point at which the user ordinarily functions begins lower. This downward shift in the baseline level of mood (their new 'baseline') motivates consumption of the drug to elevate depressed moods; i.e., the drug user's motivation for drug use in this stage is to relieve a negative state (Koob & Moal, 2008). This shift is marks the change in hedonic set point and the onset of homeostatic dysregulation (Koob et al., 1998). Homeostatic dysregulation is defined as the cycle of spiraling dysregulation of brain reward systems that progressively increases, resulting in compulsive drug use. Homeostatic dysregulation is clearly present in this scenario; drug use causes dysregulation of a-processes and b-processes which then promotes further dysregulation by motivating the drug user to alleviate a negative state by consuming drugs. This then leads to chronic use of drugs. The specific mechanism by

which hedonic tolerance changes hedonic set point is called counteradaptation (Chiara, 2003). It is when counteradaptation or tolerance occurs that an individual begins experiencing more severe b-processes in response to drug use and functioning below their original hedonic set point that may not be able to change, even after they stop using. Ahmed & Koob (1998) suggest that homeostatic dysregulation is a valid theory while also suggesting that while the transition to drug abuse from drug use is gradual, it may be permanent. This was found when the researchers provided two groups of rats with either short term (1 hour/session) access (ShA) or long term (6 hour/session) access (LgA) to a drug of abuse. They found that rats with ShA maintained stable levels of consumption while rats with LgA had escalating levels of intake after the fifth session of exposure ($p < .05$). They found that LgA rats took progressively higher levels of cocaine compared to ShA rats both in the first hour and overall ($p < .05$). These results by Ahmed and Koob (1998) suggest that escalated use of drugs of abuse can lead to constant raises in the hedonic set point over time, validating the idea of homeostatic dysregulation. After the rats experienced a 35 day abstinence period LgA rats returned to usage levels consistent with ShA rats, suggesting a recovery from increased cocaine use. However, reinstatement of the LgA regimen on LgA rats showed LgA rats returning to the pattern of increased usage more quickly than before. This suggests that neuro-correlates of addiction may be irreversible (Ahmed & Koob, 1998).

Motivation. The drug user is motivated to relieve negative feelings during b-process states and negative states due to change in hedonic set point; these feelings are feelings of withdrawal. During withdrawal GABA (the neurotransmitter is present in the stratum and the nucleus accumbens) levels change, dopamine levels drop below normal,

there is major recruitment of CRF systems by the HPA, individuals are more vulnerable to stressors due to chronically functioning stress systems and the hippocampus (a part in the brain that promotes the memory of highly emotional events and cues) promotes cue-induced cravings (LeDoux, 1998). Together these withdrawal symptoms provide a powerful incentive for individuals to increase drug use thereby cultivating and increasing homeostatic dysregulation and protracted involvement with drugs and alcohol.

Allostatis. Chronic deviation of regulatory systems from normal (homeostatic) operating levels due to increasing homeostatic dysregulation in a-process and b-process systems is called “allostatis” (Koob & Moal, 2006). Allostasis is considered a process that promotes stability of biological systems through adaptive change (McEwen, 1998). During normal functioning the human body is in a feedback mode where it responds to current demands in order to keep it in a homeostatic state; however, during allostasis the body instead responds to perceived demands in a feed-forward mechanism (McEwen & Wingfield, 2003). This feed-forward mechanism gets more pronounced with bigger changes in hedonic set point. It is suggested by Koob and Moal (1997) that this is why drug users experience more severe withdrawal symptoms or anxiety when they are aware that there is no access to a drug. Severe allostatic load (which refers to the consequences to the body being in an allostatic state) induces a change in set point that promotes pathological changes (Koob & Moal, 1997).

Numerous processes and mechanisms have been introduced including a-processes, b-processes, sensitization, hedonic homeostatic dysregulation, counteradaptation, incentive salience mechanisms and allostasis. These mechanisms all

contribute to transition from drug use to drug addiction and are critical in the review in the transition from use to addiction in alcohol below.

Alcohol's place in the Addiction processes introduced thus far

Alcohol is one of the drugs of abuse that initially activates dopamine in the nucleus accumbens when it is consumed (Yoshimoto et al., 1992); therefore, all of the mechanisms and theories that apply to drug/alcohol use in earlier sections of this paper apply to developing an addiction specifically to alcohol. During alcohol use, CRF from the HPA activates CRF systems in the extended amygdala while at the same time stopping production of CRF in the HPA through negative feedback mechanisms (Boron & Boulpaep, 2002). Dopamine systems and CRF systems then produce the euphoric and withdrawal effects of alcohol use (Rodriguex & Navarro, 1998).

Affective states during alcohol use. Like any drug, alcohol starts its drug use cycle in the body by producing dopamine in the VTA, providing positive euphoric effects of alcohol consumption to the nucleus accumbens (in the VTA) (Rodriguex & Navarro, 1998). This positive reinforcement accounts for the beginning part of the hedonic experience from using that is above an individual's hedonic set point (mood) (Koob & Moal, 2006). The HPA is then activated because alcohol is a stressor to the body and activates CRF systems in both the HPA and the extended amygdala (Sonne & Brady, 1999). CRF from either system results in a mood/state that is under the hedonic set point curve indicating a negative state. It is when euphoria has dissipated (or even counterbalanced by CRF systems) that the CRF causes the negative affective state region of the curve to predominate (Koob & Moal, 2003). During initial alcohol use this negative affective state is minor compared to the predominant jump in affective state, but

as drug use continues the negative affective states starts to predominate (Koob & Moal, 2006). The change from long positive/short negative affects to short positive/long negative affects leads to a gradual change in hedonic set point that can become a chronically changing mechanism through allostatic (or feed-forward) processes (Koob et al, 1997).. This is known as addiction.

Neurobiological risk factors. There are several neurobiological risk factors that play a role in the vulnerability of alcohol addiction aside from the mechanisms outlined above. One factor that can play a strong role in the administration of alcohol is the inner workings of the hippocampus. The hippocampus is a part of the brain responsible for memory that preferentially records highly emotional events (LeDoux, 1998). LeDoux suggested that if drug administration becomes emotional (which is highly possible due to euphoria an individual experiences during drug use), certain contextual cues would start being associated with drug administration in the hippocampus. When contextual learning cues are learned/reinforced from drug administration, the vulnerability of alcohol intake (the likelihood a user will consume alcohol) is higher when exposed to those cues (Sinha, 2008). Stress can also increase vulnerability of drug intake because activation of CRF stress reactions promotes drug use in order to alleviate the negative affective state brought on by stress (Koob, 1996). This suggests that CRF may be reinforcing the likelihood of self-administration of drugs (Sinha, 2008).

In fact, Sinha (2008) argued that the presence of glucocorticoids during the development of offspring can alter their HPA-CRF development, thereby suggesting the validity of the idea that CRF is reinforcing administration of drugs by testing rats undergoing maternal separation. Sinha (2008) showed that rats who experienced

continuous maternal separation after birth had higher levels of stress (and also self administered drugs at a higher rate) in adulthood than ones that did not experience maternal separation. This suggests that the early adverse event of maternal separation can alter CRF levels enough over the lifetime to effect the self-administration of drugs. Contextual learning and stress can also play a role in the vulnerability of drug relapse after a period of abstinence for the same reasons they promote initial drug addiction (LeDoux, 1998). Surprisingly, however, it is mainly the dysphoria, depression, irritability and anxiety (cause by b-processes) symptoms that cause relapse after abstinence, not physical discomfort (Koob & Moal, 2006).

Genetics also plays a major role in the vulnerability of drug addiction. Schepis (2011) suggested that having a family history of alcohol dependence caused adolescents to have a blunted cortical response before a challenging task. This suggests that adolescents with a family history of alcohol abuse have abnormal cortical responses which would certainly affect drug taking behavior (Ahmed & Koob, 1998). One specific genetic factor, CREB, is a transcription factor used in the central nervous system and is found at decreased levels during alcohol withdrawal (Koob & Moal, 2006). Koob and Moal (2006) reviewed that CREB alters gene expression and by proxy alters long term protein expression. While the full relationship between CREB expression and alcohol consumption is not completely understood, it is clear that CREB could possibly play a role in alcohol addiction and withdrawal. Koob and Moal (2006) also reviewed another genetic factor, NPY, which is a gene located on chromosome 4. Higher NPY provides higher stress levels to individuals which then promotes drinking at high levels to alleviate that stress. Once again this genetic factor is not well understood and only future research

can determine the relationship between these factors and the role they play in alcohol addiction and withdrawal.

Conclusion

This paper has attempted to explain alcohol addiction through the neurobiological mechanisms of drug use and abuse. Understanding the physiology behind stress response systems is key in comprehending drug addiction from this perspective; the HPA and extended amygdala's stress responses contribute greatly to the a-process (mesocortolimbic dopamine system acting on the extended amygdala) and b-process (HPA's activated CRF systems) mechanisms that explain drug and alcohol addictions (Koob & Moal, 1997). These a-process and b-process mechanisms along with the idea of homeostatic dysregulation of the hedonic set point, initial sensitization from drug use with counteradaptation following, allostasis and its feed-forward processes and effects of withdrawal all contribute to drug addiction from moderate to severe drug use. Likewise, genetic factors and hippocampus functioning contribute to the vulnerability of drug addiction and relapse after an abstinence period (Koob & Moal, 2006). Future research should focus on understanding the genetic factors that contribute to alcohol use and abuse in order to provide more effective treatment for those suffering from alcohol dependence.

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