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Alcohol Effects on Stress Pathways: Impact on Craving and Relapse Risk

Effets de l'alcool sur les trajectoires du stress : impact sur l'état de manque et le risque de rechute

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Abstract

A significant amount of neurobiological research regarding the development of alcohol use disorders (AUDs) has focused on alcohol-related activation and long-term alterations in the mesocortical dopaminergic reward pathways. However, alcohol does not only interact with brain reward systems. Many of its acute and chronic effects may be related to allostatic adaptations in hypothalamic and extrahypothalamic stress regulation pathways. For example, acute binge intoxication is associated with hypothalamically driven increases in blood cortisol, norepinephrine, and sex steroid metabolite levels. This may contribute to the development of mesocortical sensitization to alcohol. Furthermore, chronic alcohol exposure is associated with systemic dysregulation of the hypothalamic pituitary adrenal axis, sympathetic adrenal medullary system, and sex steroid systems. This dysregulation appears to manifest as neuroendocrine tolerance. In this review, we first summarize the literature suggesting that alcohol-induced alterations in these hypothalamic systems influence craving and contribute to the development of AUDs. We note that for women, the effects of alcohol on these neuroendocrine stress regulation systems may be influenced by the rhythmic variations of hormones and steroids across the menstrual cycle. Second, we discuss how changes in these systems may indicate progression of AUDs and increased risk of relapse in both sexes. Specifically, neuroendocrine tolerance may contribute to mesocortical sensitization, which in turn may lead to decreased prefrontal inhibitory control of the dopaminergic reward and hypothalamic stress systems. Thus, pharmacological strategies that counteract alcohol-associated changes in hypothalamic and extrahypothalamic stress regulation pathways may slow the development and progression of AUDs.

Abrégé

Une portion significative de la recherche neurobiologique sur le développement des troubles liés à l'alcool (TLA) a mis l'accent sur l'activation et les altérations à long terme, liées à l'alcool, des voies mésocorticales dopaminergiques de récompense du cerveau. Toutefois, l'alcool n'interagit pas seulement avec les systèmes de récompense du cerveau. Nombre de ses effets aigus et chroniques peuvent être liés aux adaptations allostatiques dans les trajectoires hypothalamiques et extra-hypothalamiques de régulation du stress. Par exemple, l'intoxication par beuverie aiguë est associée à des hausses des taux sanguins de cortisol, de norépinéphrine, et des métabolites stéroïdes sexuels, d'origine hypothalamique. Ceci peut contribuer au développement d'une sensibilisation mésocorticale à l'alcool. En outre, l'exposition chronique à l'alcool est associée à une dysrégulation systémique de l'axe hypothalamo-hypophyso-surrénalien, du système sympathique médullaire surrénal, et des systèmes de stéroïdes sexuels. Cette dysrégulation semble se manifester comme une tolérance neuroendocrinienne. Dans cette revue, nous résumons en premier lieu la littérature suggérant que les altérations induites par l'alcool dans ces systèmes hypothalamiques influencent l'état de manque et contribuent au développement des TLA. Nous observons que pour les femmes, les effets de l'alcool sur ces systèmes de régulation du stress neuroendocrinien peuvent subir l'influence des variations

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rythmiques des hormones et des stéroïdes au cours du cycle menstruel. Deuxièmement, nous discutons de la manière dont les changements de ces systèmes peuvent indiquer la progression des TLA et le risque accru de rechute chez les deux sexes. Spécifiquement, la tolérance neuroendocrinienne peut contribuer à la sensibilisation mésocorticale qui à son tour peut entraîner un contrôle inhibitoire préfrontal diminué de la récompense dopaminergique et des systèmes de stress hypothalamique. Donc, les stratégies pharmacologiques qui contrecarrent les changements associés à l'alcool dans les trajectoires de régulation du stress hypothalamiques et extra-hypothalamiques peuvent ralentir le développement et la progression des TLA.

Keywords
alcohol, allostasis, autonomic, craving, hypothalamic pituitary adrenal axis, hypothalamic pituitary gonadal axis, prefrontal cortex, relapse

Recent statistics suggest that North Americans consume 50% more alcohol than the global average and engage in higher rates of detrimental binge drinking than residents of most European countries.[1] In addition, between 7% and 10% of North Americans suffer from current alcohol use disorders (AUDs).[2] Two core features of AUDs are craving and relapse. Craving can be described as a multifaceted phenomenon that incorporates the appetitive drive for reward, the need for reduction of associated physiological distress, and a compulsive motivational state characterized by strong intent with or without loss of control.[3] Colloquially, craving is defined as an intense urge or abnormal yearning/longing[4] and is often cited by those with AUDs as the reason for relapse.[5] Relapse is defined as a return to any drinking (or, more significantly, a return to heavy drinking) after a defined period of abstinence.[6] Although the importance of craving in the clinical experience of AUDs cannot be denied, its precise physiological and neurobiological underpinnings remain unclear. Historically, measures of craving have not been consistently associated with relapse in empirical studies.[7,8] For this reason, it was not included in Diagnostic and Statistical Manual of Mental Disorders (DSM) editions I to IV. However, it was added to DSM-5 as a symptom of substance use disorders,[9] partially because with the new developments in methodology (such as ecological momentary assessments and refined laboratory and neuroimaging approaches), there is a clear link to craving, its neurobiological underpinnings, and it association with predicting future alcohol and drug use and relapse.[10]

Traditionally, the neurobiological literature on the development of AUDs has focused on the indirect and direct effects of alcohol on mesolimbic and mesocortical dopaminergic pathways.[11] In brief, the centrality of dopaminergic pathways in theories of AUD development is based, in part, on the following empirical evidence. Dopaminergic neurons in the ventral tegmental area (VTA) are directly activated by alcohol[12,13]; these dopamine (DA) neurons project to the medium spiny neurons of the ventral striatum (VS), including those of the nucleus accumbens (NAcc) that express dopamine D2 receptors (D2Rs).[14] Animal studies have shown that this sharp increase of DA in the VS underlies the initial positively reinforcing effects of alcohol: these phasic bursts of activity from VTA DA neurons in response to alcohol consumption increase the firing of afferents of the NAcc, which, in turn, is associated with the positive reinforcing effects of drugs of abuse.[15] In addition, preclinical studies have shown that alcohol also binds at allosteric modulation sites of gamma amino butyric acid (GABA) receptors; this binding is associated with prolonged chloride channel openings and inhibition of postsynaptic cells.[16] GABAergic inhibition within cognitive, emotion regulation, and motivational circuits throughout the cortex and midbrain have been linked to the sedative and negatively reinforcing effects of alcohol.[17] Ultimately, the negatively reinforcing effects of alcohol consumption that are associated with GABAergic activity might also be encoded as positively valenced by influencing dopaminergic transmission in the VTA during rewarding processes.[18]

However, preclinical studies also indicate that alcohol directly affects the functioning of the hypothalamic pituitary adrenal (HPA) axis, the sympathetic adrenal medullary (SAM) system, and the hypothalamic pituitary gonadal (HPG) axis.[19-21] These effects of alcohol on stress pathways are known to influence activity in dopaminergic pathways, but stress system activation may not only be important because of these indirect effects on DA release. In this review, we assess the literature suggesting that the fast and direct coactivation of the reward systems and core hypothalamic systems may be relevant in the increase in frequency and escalation of alcohol intake and thereby contribute to the development of AUDs. Taken together, the literature reviewed in this article suggests that 1) the experience of craving may be related to the development of mesocortical reward sensitization and co-occurring neuroendocrine tolerance in the HPA axis, SAM system, and HPG axis and 2) allostatic adaptations in these systems in response to binge and heavy drinking may contribute to a state of incentive sensitization and increased risk of relapse. Thus, medications that impede the development or progression of mesocortical sensitization and neuroendocrine tolerance may be useful in the treatment of AUDs.

Acute Alcohol Intake Activates Stress Regulation Systems

Preclinical studies suggest that several aspects of the physiological response to acute alcohol are linked to alcohol's direct activation of neurosecretory cells of the

hypothalamus.[22] Intracerebroventricular infusion of alcohol activates neurons of the paraventricular nucleus (PVN) to produce corticotropin-releasing factor (CRF), or corticotropin-releasing hormone (CRH) in humans, which enters the portal blood vessels that link the hypothalamus to the anterior pituitary gland.[23] The CRF binds to corticotropin-releasing factor receptor 1 on pituitary corticotropes, inducing the release of adrenocorticotropic hormone (ACTH) into the circulation. ACTH then stimulates the adrenal cortex to synthesize and secrete glucocorticoids (corticosterone in rats, cortisol in humans). Animal models of acute intoxication indicate that this glucocorticoid release facilitates VS reward activation.[24] These stimulatory effects are potentially enhanced by the SAM system activation that results from alcohol's effects on both the VS and PVN. Specifically, CRF release by the PVN induces excitatory signals to the sympathetic ganglia that synapse with the adrenal medulla.[25] This excitatory signal causes the release of acetylcholine in the adrenal medulla, which triggers the release of noradrenaline (NA) into the bloodstream.[26] NA increases blood pressure, triggers the release of glucose from energy stores, and increases blood flow to skeletal muscles. Thus, NA release contributes to the peripheral stimulatory effects of acute alcohol exposure.[27]

In humans, acute alcohol intake has historically been associated with elevated ACTH, cortisol, and norepinephrine (NE) levels.[28-32] However, these early studies involved administration of moderate to large doses of alcohol, with achieved blood alcohol content (BAC) at or above 0.08%. Other data suggest that ACTH, cortisol, and NE response to acute alcohol might depend on the dose, family history of alcoholism, and acute stress. For example, some data suggest that greater stimulatory effects of mild intoxication (BAC = 0.06%) are seen in individuals with a positive family history for alcoholism (FHP) than in those without FHP.[33] Other data suggest that mild alcohol intoxication (average BAC = 0.067%) does not raise cortisol or ACTH levels but can inhibit HPA axis response to cortisol administration.[34] Thus, the effect of acute alcohol on the HPA axis in healthy individuals might depend on acute stress levels. Participants with FHP without AUDs experience greater stress-related craving and consume more alcohol in response to stress than those without FHP.[35,36] Furthermore, 1 study showed that mild alcohol intoxication (average BAC = 0.066%) resulted in blunted HPA axis activity relative to placebo in healthy participants without FHP and there was no difference in HPA axis activity in healthy individuals with FHP.[37] This same study, however, showed an increased cortisol to ACTH ratio after alcohol consumption in all participants, suggesting that measures of adrenal sensitivity might be more indicative of HPA axis activation to acute alcohol than measures of cortisol or ACTH alone.

Finally, acute alcohol intake is associated with HPG axis activation in both animals and humans, although the mechanism by which it influences neurosecretory cells of the hypothalamus to release gonadotropin-releasing hormones is unclear.[38-40] The presence of these hormones in the bloodstream influences the release of neuroactive steroids from the gonads into the circulation. Neuroactive steroids are metabolites of progesterone and testosterone and act on neural tissue directly.[41] Neuroactive steroids are highly potent (at nanomolar concentrations), positive allosteric modulators of $GABA_A$ receptor function.[42] When bound simultaneously with GABA, neuroactive steroids increase the frequency of channel opening and the duration of the open state of the $GABA_A$ receptor.[43] Because alcohol is also a positive allostatic modulator of $GABA_A$ receptors, neuroactive steroids potentially contribute to the anxiolytic properties of alcohol.[44-46]

Binge Alcohol Consumption Sensitizes Reward Pathways by Altering Stress Regulation System Function

Binge drinking is defined by the National Institute on Alcohol Abuse and Alcoholism as the consumption of 5 or more standard drinks for male individuals and 4 or more for female individuals in 1 occasion.[47] Similarly, the World Health Organization defines binge drinking as the consumption of 6 or more standard drinks in 1 sitting.[48] With regular consumption of 4 to 6 drinks, alcohol-induced allostatic overload in mesocortical and mesolimbic pathways may be perpetuated by overactivation of the HPA axis, SAM system, and HPG axis in an attempt to adjust to the physiological load and facilitate neurobehavioral adaptations to adapt to a new set point. Specifically, glucocorticoids secreted via alcohol-induced hypothalamic activation modify reward-related behaviors by stimulating mesencephalic dopaminergic transmission and increasing NE levels in the prefrontal cortex (PFC).[24] Continued alcohol use seems to sensitize striatal reward function and may intensify craving.[49] NE, along with other neuronally derived catecholamines and glucocorticoids, may support mesocortical sensitization to alcohol cues by increasing the duration, magnitude, and probability of induction of long-term potentiation (LTP).[50] LTP is one synaptic restructuring mechanism that might underlie the association between alcohol intake and its reinforcing properties, both positive and negative.[51] According to the allostatic model of addiction, a sustained increase in the tonic secretion of DA and NE may culminate in a failure to maintain homeostasis and may result in decreased functioning of the stress-related HPA and SAM systems.[52] For example, blunted ACTH and cortisol response to pharmacological challenges have been demonstrated in frequent alcohol abusers.[53] Of note, the subjective experience of acute intoxication reported by binge drinkers matches predictions based on a state of mesocortical sensitization and neuroendocrine tolerance: binge drinkers report that 1 drink increases craving and stimulation, whereas light social drinkers report that 1 drink is anxiolytic and sedating.[54]

Furthermore, severe acute intoxication, such as that associated with binge drinking, increases neuroactive steroid levels in the brain and periphery of animal models.[55,56] For example, intraperitoneal CRF and ACTH injections that mimic HPA activation in response to alcohol in rats result in increased brain and plasma levels of the neuroactive steroid allopregnanolone (ALLO), a derivative of progesterone.[57] In humans, the plasma concentration of ALLO is increased after severe intoxication,[58,59] and variation in genes that encode neuroactive steroid synthesis enzymes are associated with both the subjective alcohol effects of alcohol[60] and AUD diagnoses.[61] Notably, gender differences in HPG axis activity may result in greater sensitization to the reinforcing effects of alcohol during different menstrual cycle phases.[62] For women, the basal level of circulating neuroactive steroids varies by menstrual cycle phase. Basal circulating neuroactive steroid levels are less than 1 nM in women in the follicular phase, similar to basal levels in men.[63] However, basal levels increase as high as 4-fold in women during the luteal phase.[64] During the luteal phase then, the anxiolytic properties of acute alcohol intake may be heightened in women and learning of the negative reinforcing properties of alcohol may be enhanced.

It is important to note that frequent alcohol abusers and binge drinkers are often recruited from the college-age population, because binge drinking is an increasingly popular recreational activity for this age group.[65] However, most binge drinkers ''mature out'' of a pattern of frequent alcohol binges as they move through their 20s,[66] a fact that could potentially weaken theories regarding the role of physiological adapatation of hypothalamic systems in the transition from normative, context-driven binge drinking to sustained AUDs. Although adoption of adult social and occupational roles reduces this behavior for most young adults, a certain portion persist in frequent binge drinking. A recent longitudinal study suggested that those who persist in this behavior through their late 20s and early 30s show greater initial sensitivity to the stimulating effects of alcohol, accompanied by lower cortisol release and lower sensitivity to the sedative effects of alcohol than those who do not continue binge drinking.[67,68] Importantly, those who persist in binge drinking show this same physiological response to an alcohol challenge 6 years later at follow-up.[69] In this set of studies, one-third of the heavy-drinking participants met criteria for alcohol dependence at follow-up. Thus, current research suggests that the persistence of meoscortical sensitivity and a co-occurring low HPA axis repsonse to binge/heavy alcohol intake representative of neuroendocrine tolerance combined with neurobehavioral sensitization in mesocortical dopaminergic systems may be indicative of a transition between sucessful allostatic accomodation to binge drinking with a dominance of allostatic overload seen in severe AUDs.

After acute alcohol exposure that is limited in both dose and duration, the dopaminergic and hypothalamic systems are able to return to normal tonic functioning and maintain the ability to phasically respond to novel stimuli. This return to a basal set point occurs via allostatic processes. By definition, allostatic processes allow the brain and body to achieve physiological stability through challenges to homeostasis by altering cellular structure and function to establish a new physiological set point.[70] In the healthy basal state, the number and sensitivity of dopaminergic, GABAergic, and corticotropic receptors returns to preintoxication levels. However, binge/heavy and excessive alcohol consumption results in adaptations and wear and tear (allostatic overload) to the reward and neuroendocrine regulation circuits.[52] In summary, adaptations in these stress system mechanisms, in addition to altered dopaminergic function, may represent the pathophysiology underlying the transition from controlled to compulsive alcohol seeking in humans.[10,71]

Chronic, Heavy Alcohol Consumption Is Associated With Neuroendocrine Tolerance in Stress Regulation Systems

Chronic alcohol-related allostatic changes have also been documented in AUDs in addition to the altered stress responses to acute heavy alcohol intake. In a sample of chronic moderate to severe inpatient treatment–engaged, alcohol-dependent individuals who were abstinent for 4 weeks, we reported higher basal ACTH levels and blunted alcohol cue-induced ACTH and cortisol responses compared with healthy social drinkers.[72] Furthermore, alcohol-dependent individuals with high fasting morning basal cortisol to ACTH ratios (which is a measure of sensitivity of the adrenal glands to release cortisol in response to the ACTH signal) were more likely to relapse after treatment discharge from inpatient treatment in a prospective assessment of relapse outcomes.[73] Results indicated that elevated morning cortisol to ACTH ratios more than doubled the risk of future relapse. Such basal HPA axis hyperreactivity is associated with blunted response to stress and alcohol cues and increased craving levels, which in turn, may result in high levels of alcohol intake possibly to physiologically normalize or activate the HPA axis.[73] This is consistent with other studies that have reported an association between blunted cortisol release in response to stress and alcohol cues during early abstinence and increased risk of relapse.[74] Early abstinence is also associated with a downregulation of both the dopaminergic tone in mesocortical circuits and decreased phasic release of DA in response to alcohol consumption.[75] It is important to note that decreased levels of striatal D2Rs persist in patients with AUDs at least for up to 4 months after alcohol detoxification.[76] These low DA levels are associated with relapse.[77] Clinically, this state of neuroendocrine and reward system tolerance may be linked to an unpleasant high arousal state with increased alcohol abstinence symptoms that is only partially mitigated by further alcohol consumption,[78] thereby continuing the cycle of alcohol intake and abstinence.

In conjunction with HPA axis dysregulation, sympathetic dominance may develop in AUDs.[79] Sympathetic

dominance over central and peripheral processes may be both developed and perpetuated via elevations of central NE in the PFC and NA in the circulation.[80] First, chronic high levels of NE, acting at α1 receptors, are thought to induce sympathomimetic states associated with withdrawal.[81,82] Second, chronic α1 receptor stimulation in the PFC is known to impair attentional processes by attenuating salient "signals" and increasing irrelevant "noise."[83] When the PFC cannot distinguish between relevant and irrelevant stimuli, mesolimbic brain regions may show greater bottom-up influence in behavior. Sustained increases in NE in extrahypothalamic regions and the PFC, therefore, decrease the ability of the prefrontal cortical pathways to appropriately inhibit habit-based responding to alcohol cues.[84] Increased NA in the circulation might further prime the brain to depend on instinctual and habit-based responding by keeping fight-or-flight bodily systems activated in the basal state. Chronic alcoholism is associated with impaired autonomic regulation characterized by high basal heart rate, reduced heart rate variability, and increased blood pressure.[85-87] The development of this tonically physically aroused state may also adversely influence neural activity by blunting the ability of the HPA axis to respond to stress and future binge alcohol exposures.

The risk of relapse is also increased by HPG axis dysregulation. For example, the increase in neuroactive steroids that occurs during acute intoxication counteracts HPA axis activation, thereby contributing to the blunted response of the HPA axis to alcohol and stress seen in AUDs.[88] Furthermore, clinical studies have demonstrated that levels of neuroactive steroids increase during binge intoxication[58,59] and then decrease significantly during alcohol withdrawal.[89] With repeated cycles of binge intoxication and withdrawal, as is characteristic of AUDs, this neuroactive steroid response may become desensitized and its protective effects during acute intoxication may become diminished. This loss may worsen the basal state HPA and SAM hyperactivity seen in withdrawal and during early abstinence.

Furthermore, chronic alcohol exposure elevates estrogen in both men and women.[90] Estrogen is known to modulate DA activity in the striatum and NAcc and is associated with higher levels of cortisol, which in turn may increase vulnerability to relapse.[91,92] For women, alcohol-induced increases in estrogen levels are potentiated during the late luteal (premenstrual) menstrual cycle phase. Thus, the late luteal phase could be a phase of increased vulnerability to cue-related craving.[93] Female individuals with AUDs showed greater ACTH blunting after alcohol cue exposure compared with male individuals with similar AUD symptomatology.[94,95] This may represent an important risk factor for women with AUDs, in view of the fact that HPA axis hyporeactivity to alcohol consumption has been associated with greater craving and a return to early drinking in those with AUDs.[96,97] High estrogen levels might therefore contribute to the blunted hypothalamic response to alcohol and to basal state hyperactivity of the HPA and SAM. Collectively, chronic alcohol exposure related changes in the HPA axis, SAM system, and HPG axis result in increased neuronal signaling of glucocorticoids and catecholamines that interact to dysregulate the PFC,[98] the area of the brain responsible for inhibiting emotion- and habit-based responding to interoceptive and environmental alcohol cues.[99]

Allostatic Overload Decreases Prefrontal Regulation of Stress Pathways

The PFC is critical for adaptive coping via executive control of behavior through higher-order functions such as planning, working memory, inhibition, and abstract reasoning.[100] AUDs are associated with stress-related decreased PFC function and deficits in behavioral flexibility, emotion regulation, and cognitive control.[101] In healthy individuals, the PFC modulates alcohol cue responsivity and craving via its regulatory influences on the hypothalamic PVN and thus autonomic system activity.[102-104] The PFC has also been shown to inhibit PVN activity via the GABAergic interneurons of the bed nucleus stria termanalis.[105] Its output could therefore decrease HPA and SAM responses to alcohol cues, including acute alcohol intake.[106] However, as noted earlier, alterations in the HPA axis, SAM system, and HPG axis interact to take the PFC "off-line" via sustained excess glucocorticoid and catecholamine release; these molecules modulate ionic regulation of microcircuits,[107] resulting in a failure to maintain homeostasis and a concomitant decrease in the function of normal reward and stress-related neurocircuitry.[52,108] Furthermore, chronic basal cortisol exposure maintains excitotoxic cascades that result in decreased dendritic length and decreased spine density of the dendrites in the PFC.[109] These structural changes may underlie PFC dysfunction that may manifest not only as reduced cognitive function basally but also as a loss of self-directed behavior that may be replaced by habit and sensory-driven automatic responding.[110] Recent findings from our laboratory support this notion by documenting that disrupted PFC function in the neutral-relaxed state and in response to alcohol or stress cues is predictive of a shorter time to future relapse in abstinent, treatment-engaged, alcohol-dependent individuals.[111] Importantly, this disrupted PFC function appears to mediate the relationship between earlier reported adrenal sensitivity and future relapse risk (unpublished observation). The associated lack of top-down inhibition may result in increased craving and a resumption of drinking behavior in newly abstinent patients.[112] Resumed consumption of alcohol then worsens autonomic and HPA axis dysfunction, making the next recovery attempt more difficult.[113]

Future Research to Target Hypothalamic and Extrahypothalamic Stress Regulation Systems in Treatment of AUDs

In summary, this review suggests that alcohol-induced HPA, HPG, and SAM system dysfunction promotes and

contributes to sensitized mesocortical dopaminergic reward circuits to influence craving and the development of AUDs. With chronic alcohol consumption, a decreased influence of prefrontal executive control over stress and reward systems may result in increased craving and a greater susceptibility to habit-based maladaptive coping (that is, relapse to drinking behavior).[112] Resumed consumption of alcohol may eventually lead to decreased reward functioning and neuroendocrine tolerance. The allostatic overload in these systems may weaken the regulatory influence of the PFC over hypothalamic and extrahypothalamic stress and reward circuits.[113] Therefore, pharmacotherapies that stabilize PFC dysfunction directly or indirectly might be efficacious in the treatment of AUDs. Alternatively, medications that normalize HPA, HPG, and SAM axis functioning may also restore PFC functioning and prove of benefit in alcohol relapse prevention. One of the three currently approved medications for the treatment of AUDs, naltrexone, is thought to decrease craving and self-reported high by modulating opioid activity in dopaminergic reward pathways.[114] However, these drug effects may also derive from naltrexone's normalization of the HPA axis activity in the basal state and in response to acute alcohol.[115,116] Future research that tests the effects of drug treatments on alcohol-induced hypothalamic stress systems may clarify not only the interaction between naltrexone and the HPA axis but also the role of hypothalamic and extrahypothalamic stress regulation systems in the development and progression of AUDs.

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