



Origins of Addiction Predictably Embedded in Childhood Trauma: A Neurobiological Review

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The seeds of addiction are typically sown years prior to the onset of addictive substance use or engagement in addictive behaviors, due to the priming of the reward pathway (RewP) by alterations in the mechanism of stress-signaling from the hypothalamic-pituitary-adrenal axis (HPA) and related pathways. Excessive stress from a single-event and/or cumulative life experiences during childhood, such as those documented in the Adverse Childhood Experiences Study, is translated into neurobiological toxicity that alters the set-point of the HPA axis and limbic system homeostasis [suggested new term: regulation pathway (RegP)]. The resultant alteration of the RegP not only increases the risk for psychiatric and physical illness, but also that for early onset and chronic addictions by dysregulating the RewP. This paper reviews the interface of these symbiotic pathways that result in the phenotypic pathology of emotional dysregulation, cognitive impairment, and compulsive behaviors, as well as morbidity and shorter life expectancy when dysregulated by chronic stress.

Key Words: Childhood trauma; Reward pathway; Addiction.

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INTRODUCTION

When does addiction begin?

The origin of addiction begins much earlier than when diagnostic criteria are met for a substance use disorder (SUD) in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (see Box). The story of addiction also begins much earlier than the definition (short version) of the American Society for Addiction Medicine: a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations ... reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.¹⁾

DSM-5 revised the categories and criteria for a diagnosis of a SUD; the nine identified SUDs are further qualified as mild, moderate, severe; the qualification is based on 11 symptoms of impairment that stratify across four categories of function: 1) behavioral control, 2) social/emotional expression, 3) cognitive distortions, and 4) tolerance/

withdrawal. These categories correlate with brain nuclei that are primary components of addiction pathways.

The origin of addiction, particularly moderate and severe forms, begins most often during childhood, before any addictive substance is used or addictive behavior is stimulated. Addiction seemingly originates from exposure of normal neuropathways to toxic levels of normal neural substrates that regulate stress.²⁾ The aberration in this system can be induced by a single experience and/or an accumulation of life experiences, such as childhood trauma (CT)*, and that are perceived as overwhelmingly life-threatening, frightening, and/or inescapable [criteria for post-traumatic stress disorder (PTSD)] and that are translated into neurobiological toxicity, causing harm to the pathway intended to manage stress. When left unresolved, and especially when occurring during neurodevelopment (e.g. childhood through age 18), the altered function leads to sustained imbalance causing downstream effect to related pathways (*for the purpose of this paper, CT will be inclusive of all forms of abuse, trauma, neglect, and/or violence.).

Biological mediators of stress on physical health were minimally understood in the 1990s, although cardiac research had identified allostatic load as an independent risk factor for myocardial infarction (MI).³⁾ Similarly, depression was

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identified as a risk factor for poor outcome post-MI.⁴ The mechanism that linked MI risks and outcomes remained perplexing; the variables (e.g. allostatic load and depression) reached beyond conventionally known risk factors at the time (e.g. smoking, hyperlipidemia, obesity, etc.). Rather, a more ubiquitous influence was yet to be discovered that linked allostatic load, depression, cardiovascular disease, addiction, and numerous other poor health outcomes.

The first findings emerged from the adverse childhood experiences (ACE) Study, also in the 1990s. The ACE Study culminated findings by Drs. Felitti and Anda, who independently identified strong correlations between chronic diseases and early-childhood adversities.^{5,6} Among the list of diseases linked to the original ten ACE Study questions are autoimmune,⁷ cardiovascular disease,⁸ diabetes,⁹ obesity,¹⁰ and cancer.¹¹ Among the list of mental-health disorders linked to the same ten ACE-Study questions are chronic depression,¹² anxiety,¹³ and addiction.^{6,14}

This paper reviews: 1) the key interfaces of these pathways in normal conditions and 2) the resulting pathology from neurotoxic doses of endocrine substrates that lead to a functional collapse or enmeshment of these pathways. The blended, imbalanced pathways lead to predictable phenotypic behavioral pathology including emotional dysregulation, cognitive impairment, compulsive behavioral reactivity, which correlate with DSM-5 symptom clusters.

As these pathways converge in dysfunction (and remain untreated), the long-term effects predictably result in chronic illness, progressive psychopathology, and correlate with early death, which are well-documented and independent outcomes in both addiction and toxic stress literature.^{15,16}

PATHWAYS

Homeostasis and regulation pathway

The limbic system (LS) is the emotional engine that integrates with the corpus through the hypothalamus (HYP). The LS processes emotional understanding about internal and external influences, which can be fully conscious, subconscious, or unconscious. The LS has efferent and afferent projections with the autonomic nervous system (ANS) via the HYP. The HYP is the somatic-sensory clearinghouse of LS and integrates autonomic function into emotional processing, memory, and cognitive understanding.¹⁷ The HYP rallies to meet the daily demands of stress that are communicated through the hypothalamic-pituitary-adrenal axis (HPA).

The HPA originates in the forebrain of the central nervous system (CNS) and involves efferent and afferent communication with the corpus via the ANS, including both the parasympathetic and sympathetic nervous systems (respectively). Stress

activates pro-inflammatory markers, such as corticotropin-releasing-hormone (CRH) and/or vasopressin (VSP). CRH triggers secretion of the pro-hormone, pro-opioid-melanocortin (POMC), from the HYP and which cleaves into beta-endorphin (β -END) and adrenocorticotropin-hormone (ACTH).

β -END modulates inflammation and pain in both the CNS and the ANS. β -END effects the CNS by stimulating several structures that are densely packed with opiate receptors, including the periaqueductal gray area and the amygdala (AMY) that are implicated in pain control, particularly during inflammatory states. β -END dampens perception of pain in the CNS by inhibiting gamma-Aminobutyric acid (GABA) release, which effectively results in release of dopamine (DA).¹⁸ Interestingly, in the periphery, additional β -END production is stimulated in lymphocytes by CRH and arginine vasopressin (AVP), as well as pro-inflammatory cytokine interleukin (IL)-1,^{19,20} which results in important down-regulation or inhibitory function of both B-cell and T-cell lines. Hence, the regulation pathway (RegP) simultaneously influences the balance of pain perception and inflammation in both the CNS and periphery, which has important implications for maintenance of health.

POMC-induced ACTH secretion occurs simultaneously with β -END but through the anterior pituitary. ACTH is synergistic when VSP is present,²¹ and ACTH will-alone or with VSP-stimulate nearly instantaneous secretion of cortisol (CORT) from the adrenal cortex. A negative feedback loop will inhibit CRH secretion when CORT stimulates glucocorticoid receptors densely located in the HYP and peppered throughout the RegP. This pathway targets reduction of neuroendocrine effects of stress by decreasing the acute pro-inflammatory state and restoring homeostasis, which is fundamental to health and survival.²² The HPA originates in the HYP; therefore, it has an integral relationship with the LS and influences procurement of mental and physical health by modulatory action on the ANS.

The LS-HPA is the emotional-physical engine in all mammals that integrates input from primitive regions of the brain through the cortices (Fig. 1). It influences how we interpret and respond to emotions that are stimulated by the internal and external environments, and for humans, it also integrates automatic thoughts and judgments. It is a sophisticated pathway that simultaneously synthesizes tremendous input from internal and external experiences. Collectively, the LS-HPA will be referred to as the regulatory pathway (RegP) for the purpose of this review. The RegP is one of the few areas of the CNS that begins to fully function in utero, and its purpose is to efficiently process strong emotions while maintaining ANS homeostasis and health.²³ The HPA is an endocrine cascade,

which plays a central role as governess over other endocrine cascades,²⁴⁾ neurotransmitters,²⁵⁾ and immune-modulators.²⁶⁾ The HPA's primary function is to respond to perturbations of metabolic equilibrium, return the ANS to homeostasis, and promote health and wellness.

Survival and reward pathway

The reward pathway (RewP) has evolved in all mammals, and the contributing structures and relevant functions are well-documented.²⁷⁾ This exquisite neurocircuitry evolved to ensure survival of the species, simply by releasing DA from the nucleus accumbens (NAcc), located in the frontal stria-

Reward Pathway	STRUCTURE	Regulation Pathway
Evaluates affective value of stimulus	Cerebral Cortex	Higher-ordered thinking
Avoid consequences	Cingulate Gyrus	Cognitive flexibility, social adaptation
Links reward with context	Septal Area annex to corpus callosum	Inhibition of fear, enhancement of pleasure
Positive reinforcement of behavior	Ventral Pallidum Forebrain Substantia Innominata	
Emotional experience of behavior	Extended Amygdala Temporal Lobe Corticomедial Basolateral Bed Nucleus Stria Terminalis	Emotional tone, fight-or-flight, sociability
Learning and memory	Hippocampus Temporal Lobe	Short-term into long-term memory, navigation
	Olfactory Cortex Temporal Lobe (Uncus)	Identify odors, reception, awareness
Motivation and action, Reward perception	Striatum Forebrain Nucleus Accumbens (<i>Ventral Striatum = core + olfactory tuburcle</i>): shell, core Dorsal Striatum (Globus pallidus + Putamen)	Cognitive processing of aversion
Maintain homeostasis	Hypothalamus Forebrain Mammillary Bodies Ventromedial Nucleus Lateral Hypothalamic Area	Maintain homeostasis
	Olfactory Bulb Forebrain	
Modulates mesolimbic system (feeding, energy, arousal, and metabolism)	Thalamus Forebrain	Motor control, sensory stimuli synthesis
Positive reinforcement for survival 	Ventral Tegmental Area Midbrain	Positive reinforcement for survival
Primitive stress detection	Nucleus Incertus Pre-pontine Hindbrain (midline periventricular central gray)	Primitive stress detection, regulates hypothalamic tone
	Pituitary Gland Brain—Base	Regulate endocrine system
	Brain—Corpus Distinction	
	Autonomic Nervous System Sympathetic Parasympathetic	
	Adrenal Cortex	Mobilizes substrates needed by the body during stress

Fig. 1. Reward pathways and regulation pathways. Copyright © Susie Wiet, MD 2016.

Table 1. Reward pathway

Pathway	Structures	Reward behavior	Addictive behavior
Ascending (mesolimbic)	Ventral tegmental area to nucleus accumbens (shell, core)	Desire to repeat a behavior	Craving a drug or behavior
Descending	Extended amygdala to ventral tegmental area	Emotional intensity linked to a behavior or experience	Intoxication linked to a drug, behavior, or experience
Further ascending	Core nucleus accumbens to ventral pallidum Shell nucleus accumbens to prefrontal cortex to core nucleus accumbens	Positive reinforcement of behavior	Negative reinforcement of a drug-associated behavior
Interneuron	Ventral tegmental area	Reinforcing positive reinforcement	Reinforcement of negative reinforcement of drug use

tum. A simplified summary of these pathways includes: 1) ascending pathway [mesolimbic: ventral tegmental area (VTA) to the NAcc, DA dominance]: the classical system referenced in reward/addiction that results in wanting to repeat a behavior (to ensure survival), 2) descending pathway [bed nucleus of the stria terminalis (BNST) to the VTA, opioid dominance]: producing the intensity of an experience, 3) further-ascending [NAcc to ventral pallidum, GABA and glutamate (GLU) dominance]: resulting in reinforcement of behavior, and 4) interneuron (VTA, opioid dominant): additional positive reinforcement (Table 1). In normal conditions, these circuits enhance learning and promote survival.

Reward+predictive cue→strong reinforcement

Expanded efferent and afferent feeds of the RewP integrate emotions, thoughts, and behaviors, which are similar functions of the RegP (Fig. 1). A simplified view of the RewP function includes: 1) the extended-amygdala (EAM), which is pertinent for reward perception²⁸⁾ and integrating ever-changing emotional states.²⁹⁾ The EAM influences both the s-NAcc (shell) and the BNST [via CRH, dynorphin (DYN), and norepinephrine (NE)], as well as the HYP and spinal column through the ANS, 2) the striatum [STR, ventral (v-) and dorsal (d-)] and thalamus (THAL) mediate energy and arousal states. 3) the prefrontal cortex (PFC), vSTR, and hippocampus (HIP) (implicated in memory) are pertinent for 'cueing,³⁰⁾ that influences repetition or avoidance of behavior;³¹⁾ This can be simplified by looking at survival as the integration of three fundamental aspects of the human condition: emotions, thoughts, and behaviors.

IMPACT

Childhood trauma and the regulatory and reward pathways

Addiction is well-known to be associated with the diagnosis of PTSD and has been well-documented in studies of vet-

erans.³²⁾ Many veterans have life-long struggles with addiction that resulted as compensatory survival responses to the unbearable symptoms of PTSD. In the late 1990s, PTSD literature described CT as a highly correlative risk factor for onset of combat-related PTSD,^{33,34)} versus the onset of combat-related-only PTSD. Studies also support onset of addiction as a significant predictor of a history of CT when combat-related PTSD has been diagnosed.^{35,36)}

Childhood trauma+combat-exposure→PTSD
└─┬─▶ addiction

These studies suggest delayed onset of addiction that is triggered by additional insult to the RegP leading to PTSD, that perhaps overloaded remaining resiliency traits that had previously defended the RewP. Readily available addictive substances and/or environmental cueing (other veterans using) were likely contributing factors to initiation of addictive substances.

Etiology of addiction due to CT is the confluence of a dysregulated RegP, which gives rise to pathology in the RewP.³⁷⁾ CT-related stress upregulates normal function of the RegP, including neuroendocrine modulators associated with the HPA. The RegP attempts to quell acute spikes of stress, while managing an overall upregulated pathway. Higher-ordered thought processes are neurochemically dissociated from the overrun LS-HPA circuitry. Clinically, the LS hijacks emotional processing of stress disallowing cognitive awareness, perhaps as an attempt to protect for survival.

The pathology caused by CT is in part caused by chronic bombardment of CRH, which is ubiquitously released throughout the CNS and has profound downstream effects on RegP and major endocrine cascades.^{38,39)} Though an admirable attempt, these changes result in a sustained pro-inflammatory state mediated by chronic release of CRH, which is detrimental to health⁴⁰⁾ and is implicated in many chronic illnesses. This is not unlike adaptation in other organ systems. For example, the pancreas will adapt to manage an acute elevation of glucose by increasing insulin production that will

return circulating glucose to a homeostatic level. However, if glucose is chronically elevated, the pancreas will eventually be unable to keep up with insulin production to meet the demand. Insulin resistance then ensues and causes significant downstream effects on the function of other organs and

systems. Repetitious, toxic stress taxes the HPA resulting in metabolic disequilibrium and decreased immune function. Indeed, in lieu of HPA dysregulation, chronic illnesses arise from pro-inflammatory states that stress unique genomic vulnerabilities that may otherwise lie dormant.⁴¹⁾

ADDICTION	Reward Pathway	STRUCTURE	Regulation Pathway	TOXIC STRESS
Loss of empathy	Evaluates affective value of stimulus	Cerebral Cortex	Higher-ordered thinking	Irrational behavioral responses
		Cingulate Gyrus		
		Septal Area		
Dysphoria (withdrawal), hyper-excitability, depression, stress, isolation		Extended Amygdala Temporal Lobe Bed Nucleus Stria Terminalis	Emotional tone, fight-or-flight, sociability	Dysphoria, anger-reactivity, fear, hypervigilance, anxiety
		Hippocampus Temporal Lobe		
		Olfactory Cortex		
Binge and intoxication, hedonic tone	motivation and action reward perception	Striatum Forebrain Nucleus Accumbens: shell, core	Cognitive processing of aversion	Automated (destructive) behaviors, anhedonia
		Hypothalamus Forebrain Other nuclei of the hypothalamus Paraventricular Nucleus		
Impaired immune, gastrointestinal, endocrine and cardiovascular, CNS and ANS function	Maintain homeostasis	Olfactory Bulb Forebrain		Impaired immune, gastrointestinal, endocrine and cardiovascular, central nervous system and autonomic nervous system function
		Thalamus Forebrain		
		Ventral Tegmental Area Midbrain		
Relapse (negative reinforcement; stress-induced craving)	Positive reinforcement for survival	Nucleus Incertus	Positive reinforcement for survival	Negative reinforcement (numb-out emotions)
		Pituitary Gland Brain—Base		
Hyper-/Hypo-CORT		Blood-Brain-Barrier	Regulate endocrine system	Hyper-/Hypo-CORT
		Autonomic Nervous System		
		Adrenal Cortex		

Fig. 2. Addiction and toxic stress pathways. Copyright © Susie Wiet, MD 2016. CORT: cortisol, CNS: central nervous system, ANS: autonomic nervous system.

The circuitry implicated in addiction are perturbations of the RewP that are embedded in subcortical structures of the medial forebrain bundle spanning the ventral forebrain and ventral midbrain.⁴²⁾ The disease state of addiction arises from damage to and/or dysregulation of the RewP, resulting in maladaptive learning^{28,43,44)} and compromised health that can lead to early death (not unlike that associated with ACE-Study scores). In rat models, chronic administration of addictive substances results in activation of the RewP, which also produces changes in the RegP that are congruent with the effects of CT. This is not surprising, given that both pathways share the same neuroanatomical structures and some overlapping associations during homeostasis (Fig. 2). Symptoms associated with addiction that arise from dysregulated areas of the RewP include: 1) repetitive seeking (ventral pallidum⁴⁵⁾), 2) impulsivity (PFC), 3) mood instability and emotional reactivity (VTA-NAcc-EAm), 4) pain sensitivity (NAcc), and 5) somatic complaints (HPA reset point⁴⁴⁾). Controllable stress can enhance learning for females (vs males) and is associated with cognitive resilience; conversely, males (vs females) tend to manage adverse stress more readily, making them more emotionally resilient.⁴⁶⁾

CT (and other major stressors) induces substantial release of POMC from the HYP, which simultaneously induces excessive secretion of ACTH and β -END.⁴⁷⁾ The latter stimulates the VTA (densely rich in opioid receptors) and induces the RewP, which simultaneously reinforces activation in the EAm,⁴⁸⁾ causing a loop effect of reinforcement (remaining in the midbrain-forebrain-temporal lobe) of emotional memory and dissociates conscious memory from behavior and emotions (e.g. conscious awareness is likely no longer integrated, which is observed clinically). Such internal experiences coupled with a desire to escape from the 'unthinkable' sets up a neurobiological invitation to addictive substances and behaviors. These actions flood the VTA-NAcc pathway and provide temporary relief through endogenous opioid reinforcement but at the expense of additional dysregulation⁴⁹⁾ and further dissociation from conscious awareness of the 'unthinkable.' Clinically, dysregulation in both pathways synergistically contribute to symptoms prevalent in traumatic stress disorders.

More recently, POMC has been identified as playing a significant role in addiction. However, POMC is not typically secreted as part of the RewP, from which addiction arises. Substantial and chronic release of POMC seemingly primes the RewP likely by the effect of END stimulation of the VTA, which causes disinhibition of DA release and hyper-polarizes DA receptors (DAR) within the LS, including the EAm. β -END release (from POMC-induced CRH) affects the 1) ascending pathway (mesolimbic, DA dominance) and is im-

pllicated in craving an addictive substance^{50,51)}; 2) descending pathway (opioid dominance): producing intoxication²⁹⁾; 3) further-ascending (GABA and GLU dominance): resulting in reinforcement of behavior^{52,53)}; and 4) interneuron (VTA, opioid dominant): changing to negative reinforcement in addiction.⁵⁴⁾

Addictive substances stimulate the same s-NAcc structure but release excessive DA, which results in hyperpolarization of the DAR. Repetitive stimulation leads to decreased sensitization of the DAR, likely due to DYN-another key endogenous opioid binding and modulating DAR function. When dysregulated by addiction, behavior is overly reinforced and results in compulsively focused motivation to achieve the same s-NAcc release⁴³⁾; however, that same level of stimulation is never again achieved despite the compulsivity of desire that results to experience it again. The pursuit becomes a fixated, semi-conscious compulsion coupled with dysphoria (hedonic tone) when the receptors of the VTA, s-NAcc, EAm are not saturated. Indeed, well accepted triggers for relapse include: 1) familiarity of situation, 2) availability of/access to addictive substance, 3) distress (extremes of positive and negative emotions), and perhaps 4) psychiatric instability-all triggers that are mediated by dysfunctional neurobiology.

In severe emotional dysregulation from CT (without exposure to addictive substances), a similar behavioral pattern to addiction and relapse can arise that is analogous to a psychodynamic term, repetition compulsion (RC). This maladaptive behavior pattern is emotionally-driven but unconscious. RC is typically stimulated by intense emotion, distress, contextual cues (e.g. location, time of year, etc.), or situation familiarity that induces unconscious reengagement of traumatic-like experiences. For example, a person who has experienced severe CT and has vowed to have a better life enters into revolving relationships that are demeaning and abusive but cannot seem to disengage from the repetitious cycle. To the outsider, the neurobiological pathology of the RegP is not visible, but the resulting maladaptive behavior is often interpreted as a form of addiction (e.g. "they are addicted to bad relationships"). Intensive trauma-resolution therapy can be life-saving and assists with reuniting the LS-HPA with conscious awareness (disallowing compulsive, unconscious behavior).

Similarly, other behavioral addictions (including food, pornography, sex, etc.) share similar neurobiological pathology that results in a pattern of abnormal behavior that is cued by the same challenges of relapse: distress (intense emotion), contextual cues, and familiar 'drug' of choice present. Related behavioral addictions implicate neuroendocrine cascades involving the THAL³²⁾ and that arise from dysregulation of the RewP and RegP pathways.

Overlapping pathways and ligands

Upregulation of POMC and PRODYN in the arc nucleus of the HYP from CT due to chronic CRH stimulation alters neurocircuitry, brain structures and neuroanatomical function.⁴⁰⁾ These widespread changes implicate dysregulation of cognitive, emotional, behavioral, and physical health.

POMC concentration plays pivotal roles during all stages of life, beginning with embryonic life.¹⁸⁾ It can promote neurogenesis when balanced and can wreak havoc when overly stimulated by CRH. POMC naturally decreases with aging and/or exercise. It is inhibited during acute withdrawal but during long-term withdrawal it remains increased.⁵⁵⁾ This may be suggestive of a survival mechanism or preparedness to manage anticipated stress and assist with immune function through the opioid cascade.

Additional POMC circuitry includes stimulation from the EAm, which in normal states is involved in 1) induced fear conditioning, 2) anxiety-related awareness, 3) stress response, 4) social processing, 5) sexual-behavior regulation, and 6) social-situation recognition.⁵⁶⁾ In aberrant stressful conditions, POMC can upregulate intracellular c-Fos expression (via induction of transcription), such as from HPA and/or acute withdrawal stimulation. Such effects of POMC dysregulation of the HYP is implicated in: 1) increased eating, 2) increased respiration, 3) limbic excitation, 4) pain perception, 5) analgesia, 6) addiction, 7) sexual behavior, 8) learning/memory, 9) cardiovascular homeostasis, and 10) hypophysal hormone secretion.⁵⁶⁾ In the RegP, POMC cleaves to produce β -END, which has direct action at mu-opioid receptors

and modulatory action at N-methyl-D-aspartate (NMDA) receptors throughout the RegP (Table 2).

In contrast to β -END, DYN decreases DA release due to binding at the kappa-DAR (κ -DAR) with predominant effect in the NAcc and D-STR. Dynorphin is derived from the prohormone, prodynorphin (PDYN). PDYN co-releases with ACTH (anterior pituitary) and CRH (HYP) via κ -DAR. Dynorphins are involved in modulating the Rewp, processing pain,⁵⁷⁾ and memory acquisition. Interestingly, DYNs are at highest concentration in the AMY, HIP, STR, and present-but less so-in PFC,⁵⁸⁾ which are the predominant structures of the RegP, although the STR is implicated more in the Rewp. Dynorphin also modulates NMDA receptors function in the HYP,²⁴⁾ similar to β -END (Table 2).

Dynorphin is present during fetal neurodevelopment and also stimulates release of CRH and AVP from the HYP via kappa-opioid receptors throughout life, indicating a role with inflammation. Dynorphin also plays a brief non-opioid peripartum role in regulating stress/homeostasis via regulation of prostaglandins that extinguishes shortly after birth.²⁴⁾ Perhaps this evolved to prepare offspring for survival by advancing pulmonary development and as protection from the profound maternal-fetal metabolic shifts implicated during birth. The implications of maternal distress, analogous to effects of CT, causing altered expression and function of DYN on fetal development are serious and pose risk for spontaneous abortion, low birthweight, and altered neurodevelopment in offspring.^{59,60)} Indeed, decreased dendritic arborization and GLU density in the PFC and HIP is implicated, while in-

Table 2. Basic opioid function in the reward and regulation pathways

Opioid	Storage	Stress	Addiction
Dynorphin	<ul style="list-style-type: none"> Hypothalamus Striatum Hippocampus Spinal cord 	<ul style="list-style-type: none"> Corticotropin-releasing hormone stimulates dynorphin Corticotropin-releasing hormone increases expression of prodynorphin in the hippocampus and nucleus accumbens and blocks glutamate-decreases learning Kappa antagonists increase resiliency to stress 	<ul style="list-style-type: none"> Decreased dopamine release due to binding of DYN at the dopamine receptors (especially nucleus accumbens and dorsal striatum) Kappa stimulation induces stress-related craving
Beta-endorphin	<ul style="list-style-type: none"> Pituitary (released to blood/periphery) Hypothalamus (extended amygdala, mesencephalic reticular formation, periaqueductal gray matter, rostral ventral medulla) 	<ul style="list-style-type: none"> Corticotropin-releasing hormone binds presynaptic corticotropin-releasing hormone and mu-opioid receptors that inhibit GABA release, which causes excess release of dopamine Corticotropin-releasing hormone and pro-inflammatory cytokine bind lymphocytes and stimulates beta-endorphin during inflammation 	<ul style="list-style-type: none"> Increased corticotropin-releasing hormone receptors Increased corticotropin-releasing hormone release

DYN: dynorphin

crease of NAcc neuroadaptation suggests loss of inhibitory control and decreased learning.⁶¹⁾

Collectively, the endogenous opioids have neuromodulatory effects at the pre and post-synaptic stimulatory NMDA receptors, which reside throughout in the RewP and RegP structures on glutamatergic neurons located most predominantly in the HIPP, THAL, STR, and cerebral cortex.⁶²⁾ Normal stimulation of the NMDA receptor provides a mechanism for embedding memory and learning, perhaps by reinforcing the probability of repeating a behavior via interneuron stimulation in the VTA. Dysregulation in either of these pathways leads to challenges in encoding memory and learning.

Several neuropeptides are implicated in altered pathways due to dysregulation of endogenous opioid and CORT systems associated with addiction and/or CT. Neuro-Y peptide (NYP) is a prime example. NYP storage is ubiquitous throughout the cortex, AMY, HYP, and locus coeruleus and is predominantly co-located with DYN. NYP receptors are localized on or impact the function of neighboring neurons expressing GABA, GLU, CRH, and NE.⁶³⁾ This redundant mechanism gives rise to various and altered behaviors involving feeding, novelty-seeking, and cognitive function, as well as emotional regulation. A primary mechanism of central NYP is implicated in feeding behavior; and excessive stimulation of CORT in the arcuate nucleus creates a 'vicious circle' of additional NYP release that is implicated in biophysiological changes consistent with metabolic syndrome.⁶⁴⁾ Although food stimulates both peripheral and central pathways, perhaps the imbalanced mechanism involved in food addictions implicates not only NYP but also DYN^{21,65)} and is regulated by stress. Food (particularly carbohydrate-fat) is commonly known to be a replacement addiction for illicit substances and a standalone addiction associated with CT that leads to obesity, and which is clinically reported as a vehicle to control or avoid emotions.

An additional neuropeptide that deserves mention is relaxin-3 (RXFP3), which is implicated in signaling arousal, feeding, stress responses, and cognition.⁶⁶⁾ This is a recently discovered system that projects from the nucleus incertus (NucI). Although this nucleus was originally known as the 'nucleus of uncertain function,' it seems to be highly implicated in simultaneously stimulating both the RewP and RegP. The NucI is located in the hindbrain (midline pre-pontine area), which suggests a primitive role in stress modulation and behavioral adaptation. Indeed, projections are ubiquitous throughout the combined structures implicated in the RewP and RegP pathways. Importantly, the NucI has regulatory input for all structures implicated in the RewP and RegP through two mechanisms: 1) HYP-neuroendocrine modulation (stimulation of oxytocin, AVP, and CRH release)

and 2) HIPP-electrical activity (theta-wave stimulation) that regulates acute-stress-stimulus related behavior⁶⁷⁾ through GABA activity. The latter also activates c-Fos expression within limbic structures,⁶⁸⁾ implicating stress regulation and is associated with relapse in rat models through HIPP theta-wave stimulation of the AMY and entorhinal cortex.⁵³⁾ In humans, this translates into a powerful pathway of emotional-memory-induced relapse, which may be the mechanism for that which is clinically observed in normal conditions of the RegP and RewP, and which is magnified in respective LS-HPA dysregulation and addiction.

Interestingly, RXFP3 is stimulated by CRH in stress, relapse (activation of the BNST, which is part of the EAm), as well as feeding behavior.⁶⁹⁾ Also of interest is that DAR-2 receptors reside in the NI⁷⁰⁾ and interface with serotonin (5-HT) neurons in the raphe nucleus and NE neurons in the locus coeruleus,⁷¹⁾ which may give rise to related psychopathology. Perhaps the NucI is a primary stimulus for dysregulation of the RewP and RegP pathways that may prove to contain future keys for central treatment over these complex systems.

COMMENTARY

The RewP and RegP are highly integrated and share current-time activity through the same structures and are an extremely complex mixture of ligands and trajectories causing broad downstream effects. As one pathway is overloaded from chronic exposure to addictive substances (including behavior) or extreme stress, the other pathway will also become overloaded causing cumulative dysregulation in emotional, behavioral and cognitive domains that cause downstream effect on the ANS and epigenetic translation and intergenerational transfer due to dysregulation of these life-supporting systems.⁷²⁾

An important question remains as to how intervention and treatment can repair and/or restore the aberrant pathways to normal functioning. Perhaps lessons can be learned from observing patients who are in active and long-term recovery from both CT and addiction, and have seemingly improved the function of RewP and RegP pathways. Perhaps the simultaneous interface of addressing emotional dysregulation, while addressing cravings, and reworking behavior responses allow for improved normalization of these pathways that lead to building resiliency skills. The core feature of healing these pathways is based on raising conscious awareness to 1) emotional triggers and cravings, 2) irrational thoughts, 3) current behavior choices (in present-time), and 4) the new and successful behavior that had previously been averted from conscious awareness secondary to neurobiological changes. The psychodynamic interpretation as such, is that

this process creates a corrective emotional experience, which begins to improve function of the RegP and with repetition, will improve function of the RewP.

Simultaneous healing of these pathways is akin to the emotional regulation and rewarding guidance that effective parents provide to their children. External recognition and celebration of the small steps of emotional regulation encourages willingness to tackle increasingly more advanced steps in recovery and promotes normalization of the RegP and RewP. Although long-term potentiation for relapse remains due to the history of pathway dysregulation, the potential for relapse can be mitigated greatly by raising conscious awareness about the perturbations of these pathways. Conscious awareness of emotions and thoughts can lead to effective behavior choices, which supports the importance of mind-body healing through restoration of the RewP and RegP.

Conflicts of Interest

The author has no financial conflicts of interest.

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