The Neuropathology of drug dependency, withdrawal and subtle-pulse detoxification.

Addiction is a complex neurological condition, a pathology of neuroplasticity, which comprises the usurpation of normal reward systems, the rise of neurocognitive reinforcements and cues, the loss of control over compulsive behaviour, and impulsive decision-making. Neural changes related to intoxication, withdrawal and craving preoccupation, have been observed. The meso-corticolimbic system comprises pathways from dopamine (DA) neurons in the ventral tegmental area (VTA) to the dopaminoceptive targets in the (ventral striatum) nucleus accumbens (NA), and mesolimbic and prefrontal cortex (mesocortical) areas. This system is significantly responsible for the rewarding effects obtained during intoxication/binging. Although the NA and VTA are immensely important in drug reward, results also point towards the involvement of the central nucleus of the amygdala (CeA) in the reinforcing actions of nicotine and alcohol, the ventral pallidum (VP) in the motivation of drug-seeking, and the dorsal striatum in the development of compulsive drug-seeking. Although all drugs have their own pharmacological, neurotoxic, and cognitive effects, addiction as a global process is characterized by dysfunctional inhibitory control and decision-making capacities. The shift from acute drug reward to acute drug withdrawal, on a neurobiological level, recruits the extended amygdala (including the CeA and the shell of NA), a complex cluster of nuclei involved in mediating limbic and efferent motor influx, fear conditioning, and pain processing.

A common withdrawal feature of all types of drugs of abuse is the elevation in concentration of corticotropin-releasing factor (CRF) in the CeA. Corticotropin and corticosterone levels are also increased during acute withdrawal. The additional activation of brain stress systems would then provide a supplemental force in the severity of craving, other withdrawal symptomology, and vulnerability to relapse. As part of the body's impulse control, norepinephrine (NE) affects the way the brain pays attention and responds to stressful events. Persistent drug-induced craving, through stressors or environmental stimulus factors, is thought to be dependent on the activation of a glutamatergic pathway, from the medial prefrontal cortex (PFC) to the NA. The purpose of glutamate (Glu) is to elicit action, while the function of the neurotransmitter gamma-Aminobutyric acid (GABA) is to restore calm. Involvement of the basolateral amygdala and PFC in the attribution of cues and their emotional value is also likely to be decisive. Stress-induced reinstatement of drug-seeking behaviour depends largely on the sustained action of CRF in the extended amygdala. This final stage of the addiction cycle elicits the importance of the prefrontal systems in decision-making processes and cognitive control. Ultimately, the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), and anterior cingulate cortex (ACC) take into account all cues coming from the basal ganglia, amygdala, and hippocampus to determine whether or not the individual will resist the craving. Drug dependency is, therefore, a pathology of neuroadaption. It is neurobiologically determined by the modulation of dopamine transmission, and modifications in mesocortico-limbic circuitry and, subsequently, in the excitability of prefrontal cortices.

Recent research has identified the DLPFC as an important cerebral relay in normal pathological behavioural output, which makes it a target of great interest in the application of cranial electro-stimulation. Subtle pulse technology also appears to influence subcortical structures offering modulatory potential in diverse addictive disorders, including the mediation of specific withdrawal symptoms. Addiction is a chronically relapsing disorder characterized by the compulsive seeking and abuse of a substance despite its adverse and morbid effects. Cognitive impairments and deficits are common among drug-users and are consequently correlated with higher rates of relapse. Targeted subliminal electro-stimulation offers potential both of improved retention during withdrawal and reduction of recidivism. The comprehensive aim of treatment should be to resolve the whole addiction cycle from Binge and Intoxication (*High and reward sensation* involving DA systems; VTA, NA and striatum); to Withdrawal and morbid consequences (*Negative effect and depressive symptoms* involving NE and CRF; CeA and NA); to Craving and Obsession (*Preoccupation and anticipation* involving Glu and GABA systems; PFC and hippocampus). The effectiveness of non-invasive brain stimulation in addictions has been observed in the control of acute withdrawal severity and chronic withdrawal syndrome (long-term neurological deficits). Specific molecular frequencies and wavelengths may therefore be modulated in subtle pulses to deliver neural pathways from a broad spectrum of dependencies.

Abbreviations:

ACC Anterior cingulate cortex
CeA Central nucleus of the amygdala
CRF Corticotropin-releasing factor
DA Dopamine
DLPFC Dorsolateral prefrontal cortex
GABA gamma-Aminobutyric acid
Glu Glutamate
NA Nucleus accumbens
NE Norepinephrine
OFC Orbitofrontal cortex
PFC Prefrontal cortex
VP Ventral pallidum
VTA Ventral tegmental area

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