Excited Delirium and Sudden Death

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The entity, **Excited Delirium Syndrome**, has been the focus of much discussion over the past 10 to 15 years. Typically, this entity is used as the cause of death of highly agitated persons who are in police custody, who are not uncommonly restrained and or incapacitated by electrical devices. Following a complete autopsy, the forensic pathologist cannot define a specific anatomic cause of death, but frequently identifies psychostimulant intoxication, such as methamphetamine and cocaine, often in the presence of alcohol, as a contributing factor underlying causation of death.

Due to these individuals presenting in such an agitated and bizarre manner, police officers are often called to the scene. The usual course of events is after the police have witnessed their behavior, there is an effort to restrain the individual using various methods of force, such as maximal restraints, baton strikes, chemical "pepper" sprays or electrical devices. Not uncommonly, during or after the use of such methods of restraint, the individual suddenly experience a cardiac arrhythmia, which culminates in sudden cardiac death.

Pathophysiologic process which leads to sudden death in Excited Delirium Syndrome

It appears the underlying causation of excited delirium syndrome revolves around a neurohormone referred to as **dopamine.** Neurohormonal control of brain activity revolves around three neurohormonal systems: **a norepinephrine system, a dopamine system** and a **serotonin system.** What we are interested in is the **dopamine system**.

Dopamine is an organic chemical of the catecholamine and phenethylamine families that plays several important roles in the brain and body. It is an amine synthesized by removing a carboxyl group from a molecule of its precursor chemical L-DOPA, which is synthesized in the brain and kidneys.

In the brain, dopamine functions as a neurotransmitter, which is a chemical released by neurons (nerve cells) to send signals to other nerve cells. The brain includes several distinct dopamine pathways, one of which plays a major role in reward-motivated behavior. Most types of rewards increase the level of dopamine in the brain, and many addictive drugs, such as cocaine and methamphetamine, increase

dopamine neuronal activity. Other brain dopamine pathways are involved in motor control and in controlling the release of various hormones. These pathways and cell groups form a dopamine system which is **neuromodulatory.**

Neuromodulation is the physiological process by which a given neuron uses one or more chemicals to regulate diverse populations of neurons. This is in contrast to synaptic transmission in which an axonal terminal secrete neurotransmission to target fast-acting receptors on only one particular partner neuron. Neuromodulators are neurotransmitters that diffuse through neural tissue to affect slow-acting receptors of many neurons. Major neuromodulators in the central nervous system include **dopamine, serotonin, acetylcholine, histamine, and norepinephrine**.

Neurotransmitter systems are systems of neurons in the brain expressing certain types of neurotransmitters, and thus form distinct systems. Activation of the system causes effects in large volumes of the brain, called volume transmissions. Volume transmission is the diffusion of neurotransmitters through the brain extracellular fluid released at points that may be remote from the target cells with the resulting activation of extra synaptic receptors, and with a longer time course than for transmission at a single synapse.

The major neurotransmitter systems are the noradrenaline (norepinephrine) system, the dopamine system, the serotonin system and the cholinergic system. Drugs targeting the neurotransmitter of such systems affects the whole system, and explains the mode of action of many drugs.

The dopamine pathways are as follows: mescortical pathway, mesolimbic pathway, nigrostriatal pathway and the tuberoinfundibular pathway. The target of each of these pathways is the dopamine receptors at each pathway termination. The effects of activation of these pathways is on the motor system, reward system, cognition, endocrine, and nausea. **Cocaine blocks the re-uptake of dopamine, leaving dopamine in the synaptic gap longer, which in effect prolongs the effect of dopamine on those groups of neurons.**

Cocaine and methamphetamine increase extracellular dopamine and produce behavioral effects similar to mania. Mania is a state of abnormally elevated arousal, affect, and energy level, or “a state of heightened overall activation with enhanced affective expression together with lability of affect.” The heightened mood can be either euphoric or irritable; indeed, as the mania intensifies, irritability can be more pronounced and result in violence, or anxiety. Mania has multiple causes. Although the vast majority of cases occur in the context of bipolar disorder, it is a key component of other psychiatric disorders, such as schizoaffective disorder, bipolar type, and may also occur secondary to various general medical conditions, such as multiple sclerosis. Certain medications may perpetuate a manic state, for example prednisone or substances of abuse, such as caffeine, cocaine or anabolic steroids.

Drug sensitization occurs in drug addiction, and is defined as an increased effect of a drug following repeated doses (the opposite of drug tolerance). Such sensitization involves increased brain mesolimbic dopamine transmission, as well as altered protein expression within mesolimbic neurons. **It is believed the dysregulation of the mesolimbic pathway and its output neurons in the nucleus accumbens plays a significant role in the development and maintenance of an addiction.**

The specific pathway that is involved in the development of psychoses, including schizophrenia, is the mesocortical pathway, which is closely associated with the mesolimbic pathway.

Another psychological phenomenon of cocaine abuse is the development of paranoia. There is evidence to suggest, paranoia in the cocaine abuser is due to a decrease in function of the **dopamine transporter protein.**

Transporter proteins are carrier proteins involved in the movement of ions, small molecules, or macromolecules, such as another protein, across a biological membrane. Carrier portions are integral membrane proteins, that is, they exist within and span the membrane across which they transport substances. Each carrier protein is designed to recognize only one substance or one group of very similar substances. Thus, the dopamine transporter protein will only transport dopamine or very similar substances, such as amphetamine.

The dopamine transporter pumps the neurotransmitter dopamine out of the synaptic cleft back into the cytosol. In the cytosol, other transporter proteins sequester the dopamine into vesicles for storage and later release.

Cocaine blocks the dopamine transporter protein by binding directly to the transporter and reducing the rate of transport. In contrast, **amphetamine** enters the presynaptic neuron directly through the neuronal membrane or through the dopamine transporter protein, competing with the re-uptake of dopamine. Another interesting aspect of amphetamine is when it enters the vesicles which are storing dopamine, it causes dopamine's release back into the cytosol, which further allows dopamine to be available to exert its physiologic effect.

In the chronic abuse of cocaine the dopamine transporter undergoes neurobiological adaptations, with the degree of neurobiological adaptations, depending on the duration, amount and pattern of use (e.g., bing vs. daily use). Experimentally, intermittent cocaine use produces sensitization of the stimulant effects of cocaine at the dopamine transporter and enhanced locomotor responsiveness or what is termed **behavioral sensitization**. Another factor to keep in mind, since cocaine directly inhibits dopamine re-uptake by binding to the transporter, repeated cocaine administration may lead to a reduced potency of cocaine, which leads to an elevation in synaptic dopamine and the expression of behavioral sensitization. It also leads to an

increase in desire to acquire more cocaine, which is probably mediated through the mesolimbic pathway as well as the mesocortical pathway.

The **dopamine transporter** expressed in the presynaptic terminals of dopamine neurons regulates re-uptake of dopamine from the synaptic cleft and keeps extracellular dopamine concentrations low. The dopamine transporter is critical in regulating the concentration of extracellular dopamine and overall dopaminergic tone. **By blocking the transporter protein, cocaine allows released dopamine to persist in the extracellular space, which prolongs dopamine receptor stimulation. A decrease in dopamine transporter numbers or function in response to cocaine leads to reduced dopamine re-uptake, elevated synaptic dopamine, and increased dopamine signaling at postsynaptic receptors. Additionally, should the individual simultaneously take amphetamine, this will release more dopamine from the storage vesicles into the cytosol and thus making more dopamine available for signaling at the postsynaptic receptors.**

The syndrome of exited delirium in drug abusers demonstrates that cocaine is the most frequent reported illicit drug. Most drug-related excited delirium victims are chronic freebase cocaine ("crack") abusers, usually engaged in a "binge" pattern of drug use. These persons use large amounts of "crack" cocaine and/or methamphetamine often for days, which interrupts normal sleep-wake cycles. **Inhibition of dopamine transporter function is thought to be the primary mechanism underlying cocaine's addictive effects.** Although, excited delirium is most frequently reported in cocaine abusers, psychostimulants including, methamphetamine, MDMA (3,4-methylenedioxymethamphetamine, also called "Molly" or "Ecstasy"), alpha-PVP (alpha-pyrrolidinopentiophenone, also called "Gravel"), methylome (DNA methylation, the chemical process that adds a methyl group to DNA is the principal manner in which genes are transcriptionally repressed or silenced. Inserting methyl groups changes the appearance and structure of DNA, which may directly block DNA recognition and binding of transcription factors, or may attract other factors that preferentially bind to DNA to interfere with transcription factor accessibility. The process of DNA methylation creates a methylome), and ephedrine have been associated with the syndrome. These psychostimulants directly interact with the dopamine transporter to cause a marked increase in the levels of synaptic dopamine.

Persons at risk for excited delirium are most likely at the extreme end of the neuropsychiatric continuum of several recognized neuropsychiatric disorders, including delirium induced by a drug, manic excitement, and psychomotor agitation. Those at risk for excited delirium and sudden death include people who are withdrawing from or are non-compliant with psychotropic drugs, substance abusers suffering from reward deficiency syndrome or alcoholics in withdrawal, and persons suffering from acute manic episodes that may be triggered or worsened by sleep deprivation.

Cocaine related exited delirium cases typically occur in persons who have reported histories of chronic cocaine abuse, and at the time of autopsy, benzoylecgonine and or cocaine are identified in their blood and if measured, also in their brains.

All psychostimulants (e.g., cocaine, methamphetamine, MDMA, etc.) increase the synaptic levels of dopamine, which may explain why chronic psychostimulant abusers are more at risk for exhibiting the behavioral symptoms associated with excretory delirium syndrome. A central role of dopamine is to mediate a person's environmental event experiences and the internal representations they evoke in a time and stimulus-dependent neural regulation, which is a dynamic process. Dopamine can enhance both approach and avoidance behaviors and trigger extreme fear. In chronic cocaine abusers, there is a compensatory up regulation in dopamine transporter function, which is an adaptive increase to offset dopamine overflow in the synapse. **When this homeostatic control of synaptic dopamine fails, it leads to a functional hyperdopaminergia, which triggers the acute onset of delirium and marked agitation in excited delirium syndrome victims.**

The mental and emotional stress triggered by the hyperdopaminergic state is expressed in the brain as fluctuations in the activity of a subset of brain regions, including the **insula, cingulate cortex, and amygdala**. These regions serve as an interface between emotional feeling states and visceral responses of the body. **The insula and cingulate are the viscerosensory cortices, which function to regulate attention and autonomic arousal. The amygdala is important in detecting and learning threat even in the absence of conscious awareness. The insula and cingulate cortices and subcortical regions of the limbic brain are heavily innervated by dopaminergic projections from the ventral segmental nucleus.** These closely connected brain regions together with the dorsal and ventral striatum are viewed as a "salience network," acting directly on hypothalamic and brainstem centers to increase our bodily arousal state through direct coupling with sympathetic and parasympathetic efferent nuclei and feedback control loops located in the brainstem.

The insular cortex and the infra limbic cortex are part of a network involved in the descending control of the cardiovascular system. These forebrain regions are responsible for integrating emotional and cognitive aspects related to cardiovascular responses. Together with the autonomic nervous system nuclei of the brainstem, these forebrain regions regulate cardiac function and electrophysiology via direct neural influences. Thus, the roles of mental stress and emotion are in reality contributors to the pathophysiology in the genesis of centrally mediated acute cardiac arrhythmias and sudden cardiac death in excited delirium syndrome.

CONCLUSION

Elevated synaptic dopamine when coupled with failed dopamine transporter function leads to agitation, paranoia and violent behaviors associated with excited delirium syndrome. The brain's dopamine also regulates heart rate, respiration, and core body temperature with chemical imbalance resulting in tachycardia, tachypnea, and hyperthermia. Victims of excited delirium are in an extremely heightened emotional state exhibiting marked paranoia and mounting irrational fear. Abnormal signaling in the brain-heart axis may be a precipitant of a sudden fatal cardiac arrhythmia, since hyperdopaminergic signaling in the limbic system can convert extreme emotional stress into autonomic toxicity. **The connection between the hyperdopaminergia and chaotic signaling in the higher brain autonomic regulatory centers may explain the abrupt loss of autonomic function that leads to sudden unexpected death in victims of excited delirium syndrome.**

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