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***Neurobiology of Addiction-like Behaviors***

**Bockstaele. Introduction: The Neurobiology of Addiction-like Behaviors, pp. 1-3**

Domain 3: Research

SUMMARY:  Addiction remains a major public health problem and studies over the past 2 decades have improved understanding of the neural substrates underlying the biological basis of addiction-like behaviors.  However, much remains unknown and new categories of addiction such as prescription medications, food, gambling and sex are being defined.  Addiction is varied and complex and often comorbid with other psychiatric disorders.  The fields of neuroscience, genetics and psychiatry provide significant insight into the neurobiological adaptations that underlie addiction-like behavior.  Appropriate animal models are important to study addiction behavior and the contribution of gender has been emphasized in the management of addiction-related behavior as it relates to age of first use to dependence to relapse.  New emphasis has been placed on the study of these behaviors and non-drug reinforcers such as food and binge eating.  The neurobiological mechanisms that control excessive food intake and how this may be co-opted to control alcohol consumption as well as the similarities between drug addiction and obesity in functional impairment in the brain and neurotransmitter circuits are being studied. Possessing the basic knowledge of adaptive experience and dependent plasticity will lead to a better understanding of the neural circuit dysfunction in addiction-like behaviors, and enable the identification of novel targets for intervention and treatment.  In 2004, Volkow and Li re-defined addiction as a condition of dysfunctional motivated behavior rather than compulsive drug and alcohol use.  Addiction is a chronic relapsing disorder with a craving state characterized by compulsive behaviors despite consequences to self and others.  The behaviors of substance abuse include acquisition, maintenance, escalation and dependence and a genetic linkage has been shown but only explains about 50% of the risk.  Environmental stimuli and genetics determine initial responses to drugs of abuse and the transition to addiction.  Drugs and non-drug reinforcers target the mesocorticolimbic dopamine system in the nucleus accumbens and the prefrontal cortex.  The initial euphoric effects of increased extracellular dopamine engage other neural circuits that contribute to the initiation of drug-seeking activities.  Additionally, glutamate signaling is an important response to certain drugs such as amphetamine, cocaine and opiates.  Opiates and other drugs of abuse can cause homeostatic disruption of glutamate, a ubiquitous excitatory neurotransmitter.  The glutamate-opioid interactions in drug abuse may help identify new therapeutic targets for the treatment of addiction.

QUESTIONS

1. Which one is correct regarding neurotransmitters?
2. Glutamate and glycine are excitatory and GABA is inhibitory
3. Glutamate is excitatory and glycine and GABA are inhibitory
4. Glutamate and GABA are excitatory and NMDA is inhibitory
5. Glutamate is excitatory and NMDA and GABA are inhibitory.
6. Which one is correct regarding opiate receptors?
7. The Mu receptor is located in the spinal cord and has low physical dependence
8. The Kappa receptor is located in the cerebral cortex and thalamus and causes respiratory depression
9. The Delta receptor is located in the frontal cortex and limbic system and causes dependence
10. All 3 receptors are associated with respiratory depression
11. Which one is correct regarding the opiate/drug and its actions at the receptors?
12. Naltrexone is a strong Mu and Kappa antagonist
13. Morphine is a strong Delta agonist and weak Kappa agonist
14. Buprenorphine is a partial Delta agonist and weak Kappa antagonist
15. Nalorphine is a partial Mu agonist and a strong Kappa antagonist

ANSWERS

1. b

2. c

3. a

**Wu and Schulz. Advancing Addiction Treatment: What Can We Learn from Animal Studies? pp. 4-13**

Primary Species:Rat (*Rattus norvegicus*), Mouse (*Mus musculus*)

Domain 3, TT3.3

SUMMARY: Drug addiction is characterized as a disease that causes compulsive, uncontrolled drug-seeking and taking behavior.  It can be characterized by withdrawal symptoms but even in the absence of these symptoms, animals self-administer psychoactive substances for the pleasurable effects.  This is termed positive reinforcement.  This reward system is closely tied to the memory system.  When addicts begin to resume taking drugs in order to alleviate withdrawal, this is termed negative reinforcement.  Animal models of addiction should incorporate both positive and negative reinforcement.  Self-administration animal models have pinpointed dopamine as a primary mediator of brain reward pathways, as well as glutamate, γ-aminobutyric acid, serotonin, and norepinephrine which modulate dopaminergic neuronal activity.

Cocaine inhibits dopamine transporter and prevents reuptake into presynaptic systems.  A dopamine transporter (DAT) knockout (KO) mouse was created.  Cocaine-activated locomotor activity is decreased/eliminated in these animals, while self-administration patterns are less clear (found be either decreased of unaffected).  With the creation of a DAT knock-in (KI) mouse, it was found that functional DAT is necessary to maintain cocaine addiction.  Other transgenic mice for this addiction include DAT-overexpression transgenic mice, vesicular monoamine transporter KO mice, cocaine-insensitive mice, DAT-serotonin reuptake transporter double knockout mice, and dopamine-deficient mice.  A promising treatment for cocaine addiction is bromacriptine (dopamine agonist).

Amphetamines reverse reuptake of dopamine, serotonin, and/or norepinephrine in the brain.  The DAT KO mouse has shown that conditioned place preference paradigm remains intact in amphetamine use which leads to the hypothesis that the memory system may be the best candidate for treatment of this addiction.

Opioids activate release of dopamine through µ and δ opioid receptors in the nucleus accumbens and ventral tegmental area.  Animal models have shown that µ opioid receptors possess highest abuse potential.  Treatment of this addiction includes detoxification and relapse prevention using agonist replacement therapy.  For example, methadone is a common replacement medication and is typically tapered during detoxification.  Buprenorphine, buprenorphine-naloxone, and other opioid agonists have been used.

Nicotine activates brain nicotinic receptors, ligand-gated cation channels that conduct Na+, K+, and Ca+ which leads to dopamine release. Mice lacking β2, α4, or α6 nicotinic receptors do not self-administer nicotine, while α7 had no effect, and deletion of α5 or overexpression of β4 increased self-administration. Currently, there is no effective nicotine addiction therapy, but nicotine replacement therapy can ease cravings.  Preclinical studies suggest glutamatergic transmission plays a role in this addiction.

Alcohol addiction animal modeling is complicated since no single model paradigms all alcohol dependence characteristics.  Most laboratory animals do not readily consume alcohol.   The ALKO AA rat prefers 10% alcohol solution over water.  The Sardinian alcohol-preferring rat consumes more than 4g/kg 10% alcohol during first drinking session and display binge drinking like behaviors.  Marchigian Sardinian rats are phenotypically similar to Sardinian strain; they are also highly vulnerable to stress-induced relapse consumption.  Alcohol-preferring P rat line voluntarily consume 10-30% alcohol solution to point of intoxication and bar-press to self-administer with binge drinking patterns consuming 6g/kg during 1 hour access period.  The UCh-B rat line is genetically selected for high alcohol consumption but is not widely used.  Addictive properties of alcohol may be mediated by GABA neural transmission which results in a release of dopamine.  Treatments include disulfiram which prevents aldehyde dehydrogenase from breaking down giving adverse effects and opioid receptors and β-endorphin systems to modulate alcohol consumption behavior.

A better understanding of neurobiological processes involved in addiction will help develop more efficacious medications and therapies for the treatment of addiction.

QUESTIONS:

1. What is meant by positive reinforcement in addiction research?
2. Which animal model is used in both cocaine addiction research and amphetamine research?
   1. UCh-B rat
   2. Dopamine deficient mouse
   3. DAT KO mouse
   4. DAT KI mouse
3. What are the 5 alcohol addiction animal models currently available?

ANSWERS:

1. Positive reinforcement is the term for when animals self-administer psychoactive substances for the pleasurable (rewarding) effects, not dependent on counteracting withdrawal effects.
2. c. DAT KO mouse
3. ALKO AA rat, Sardinian alcohol-preferring rat, Marchigian Sardinian rat, Alcohol-preferring P rat, and UCh-B rat

**Quinines-Jenab and Jenab. Influence of Sex Differences and Gonadal Hormones on Cocaine Addiction, pp. 14-22**

Domain 3: Research; Task 1: Facilitate or provide research support; K1: animal models (spontaneous and induced) including normative biology relevant to the research (e.g., background lesions of common strains).

SUMMARY

Introduction:Cocaine abuse is on the rise among women, and drug addiction studies consistently show greater responses among females than males in various cocaine-related outcomes. This review presents a discussion of sex differences and the role of gonadal hormones as the biological basis for the sexually dimorphic pattern in behavioral responses to cocaine. Reports of human and animal cocaine addiction studies share many features and findings such as male-female differences in responses to cocaine; modulation of cocaine-induced outcomes by gonadal hormones; complex interaction of these different factors in behavioral responses to cocaine; and possible contributions of non-hormonal mechanisms that confer drug abuse vulnerability.

Male-Female Differences in Responses to Cocaine:Animal and human studies reveal sexually dimorphic patterns in behavioral response to cocaine in all phases of the cocaine addiction process from initiation to maintenance and relapse. It is possible that a female´s increased sensitivity to drug conditioned stimuli affects not only behavioral and subjective responses to cocaine but also relapse after exposure to environmental cues. Furthermore, in animal models, females require lower doses of cocaine to develop faster conditioned place preference and cocaine-induced psychomotor behaviors and sensitization. A clear picture is emerging and suggests that the biological basis of sex-specific differences in cocaine addiction lies, in part, in chromosomal mechanisms that contribute to drug abuse vulnerability.

Modulation of Cocaine-Induced Behavioral Outcomes by Gonadal Hormones: Progesterone attenuates cocaine-induced psychomotor responses, but its effects have been shown to be dose and time dependent. Whereas longer pretreatment with progesterone before cocaine administration decreases ambulation, shorter pretreatment has no effect.

Complex Interactions Between Estrogen and Progesterone in Cocaine-Induced Behavioral Responses:The interactions of many factors that affect sex differences appear to be complex. For example, in females, estradiol has facilitatory effects overall, whereas progesterone inhibits most cocaine responses. The interaction of progesterone with estrogen is also affected by the concentrations of gonadal hormones used. When coadministered at different ratios, the two hormones differentially affect locomotor responses to cocaine. Specifically, administration of high estradiol doses with high level of progesterone increases total locomotor behavior, and administration of low estradiol doses with high levels of progesterone inhibits total locomotor activity.

Possible Nonhormonal Mechanisms That Confer Drug Abuse Vulnerability:Besides sex differences, other sexually dimorphic behavioral differences such as depression, anxiety, impulsivity, and arousal may contribute to female vulnerability to cocaine abuse. Moreover, there are sex differences in the ability to cope with stress and HPA axis activations and research shows that stress-related activation of the HPA axis and stress-induced cocaine craving are key components of cocaine addiction.

Conclusion: Determination of neuronal responses that convey sexually dimorphic responses may not only advance understanding of the causes and potential treatments for addiction, but also increase the understanding of how a person´s sex may contribute to drug abuse and/or to the development and expression of other mental health diseases. There is a need to study sex differences and hormonal effects in drug addiction to understand the progression of addiction and to develop effective gender-sensitive treatments.

QUESTIONS

1.  True or False. The influence of sex differences and gonadal hormones has also been shown in the behavioral and rewarding effects of other drugs of abuse such as amphetamines, opiates, nicotine, heroin, cannabinoids, and alcohol.

2. In animal studies, which gender exhibits greater locomotor and stereotypic behaviours after acute or chronic cocaine administration in rats?

a. Female rats

b. Male rats

c. Castrated male rats

d. Spayed female rats

e. All of them are true

3.  True or False. Clinical and preclinical findings indicate that sex differences and gonadal hormones may not account for individual differences in susceptibility to the reinforcing effects of these addictive substances.

4. Critical stages of cocaine behavioral responses and self administration in animal models are:

a. Locomotor and behavioral responses

b. Initiation and maintenance

c. Escalation and bingeing

d. Extinctions and withdrawal

e. Reinstatement and/or relapse

f. All of them are right

5. Most rodent studies have shown that cocaine-induced behavioral activity after acute administration is lowest during:

a. Estrus

b. Proestrus

c. Metaestrus

d. Diestrus

ANSWERS

1. True

2. a

3. False

4. f

5. d

**Corwin and Babbs. Rodent Models of Binge Eating: Are They Models of Addiction? pp. 23-34**

Domain 3: Research

SUMMARY: This article explores whether some recently developed models of binge eating can also be considered models of food addiction.  In order to model these behavioral pathologies, valid rodent models should meet human criteria for both bingeing and substance dependence as described in the 4th edition and proposed for the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM). Binge eating has both subjective and objective definitions which include objectively the consumption of more food in a discrete period of time than would normally be consumed and subjectively a feeling of lack of control while eating.  Behavioral profiles of bingeing animals should share characteristics with those of animal models of drug addiction. This article evaluates and discusses current rodent models of bingeing, their contributions to scientific understanding of bingeing, their validity with respect to DSM criteria, and their overlap with models of addiction. The models described indicate that repeated intermittent bouts in which large quantities of fatty or sugary foods are consumed (binges) are associated with behavioral changes similar to those described for drugs of abuse. In contrast, control groups consuming the same foods in a nonbinge-type manner do not exhibit an “addiction-like” behavioral profile. Thus, fatty/sugary foods in and of themselves do not appear to have addictive qualities.  Rather, the manner in which they are consumed appears to be critical. In addition, while rodent models of bingeing and drug self-administration share similarities, the article does not support reclassifying the bingeing-related eating disorders as substance use disorders because of differences that distinguish such disorders in humans.  Eating disorders in humans are characterized by body shape and weight concerns that do not usually play a role in substance abuse disorders.

QUESTIONS

1. What criteria of human binge eating have rodent models attempted to reproduce?

2. Briefly describe the Boggiano model of bingeing.

3. Describe how the Corwin model attempts to validate the forbidden food hypothesis of human bingeing?

4. What is a commonality to all models described in this review?

5. Which of the following is a criterion for substance dependence?

a.   Tolerance

b.   Withdrawal

c.  Consumption of substance in greater amounts

d.  Increased time seeking substance

e.  All of the above

6. T/F. Rodent models have led to the discovery of unequivocal evidence for a genetic basis of binge eating?

ANSWERS

1. Eating more in a discrete time period than would normally be consumed under similar circumstances in the same period of time.   Rodent models must demonstrate large intakes of food within a defined brief period.

2. It uses cycles of energy restriction and refeeding combined with a stress component at the end of the final cycle.  Aids in modeling the contribution of stress to binge behavior.

3. It does not use energy restriction to induce bingeing; it uses intermittent limited access to palatable food to increase food intake. It also models eating in the absence of hunger as rats are never food deprived.

4. All use intermittent access to palatable food to increase intake of that food.

5. e

6. F

**Barson et al. Neurobiology of Consummatory Behavior: Mechanisms Underlying Overeating and Drug Use, pp. 35-58**

SUMMARY:Both caloric and emotional needs underlie behaviors that result in overconsumption. Animal models have been developed by genetic manipulation, selective breeding for specific traits, forced or voluntary exposure to a substance, and biomarker identification. The hypothalamus mediates energy homeostasis, but reinforcement is mediated more outside the hypothalamus by nuclei in the mesocorticolimbic regions. Orexigenic neurochemicals that control food intake can provide a general or specific signal for promoting caloric intake of a specific macronutrient. Several neurochemicals are involved in control of fat ingestion; galanin, encephalin, orexin, melanin-concentrating hormone, and the endocannabinoids. There is a positive feedback loop when fat is consumed as these peptides both increase fat intake and are further stimulated by its intake. Alcohol consumption is driven similarly by neurochemical systems involved in fat metabolism according to data that links fat and alcohol consumption. Understanding of the neurosystems involved in consummatory behavior will lead to the development of therapies targeted for the treatment of both overeating and drug abuse.

QUESTIONS:

1.What is the prevalence of obesity in this country?

2. What is unique about fat metabolism as compared to carbohydrate and protein metabolism?

ANSWERS:

1. It has more than doubled since 1980—from 14% to 31%

2. Carbohydrate and protein metabolism are negatively regulated unlike fat metabolism that is positively regulated

**Michealides et al. Translational Neuroimaging in Drug Addiction and Obesity, pp. 59-68**

Domain 3: Research; K2: research methods and equipment

SUMMARY: Ingestive behavior is a collection of acts involving the introduction of a substance into the body either by eating, drinking, injecting, smoking or snorting. Disorders such as obesity and drug addiction are influenced by similar biochemical and physiological processes and are likely a result of disturbances in ingestive behaviors. Homeostatic mechanisms involved in ingestive behavioral regulation include satiety signals including ghrelin, cholecystokinin, glucagon-like peptide and gastrin-releasing peptide; all of which are rapid in response. Adiposity signals such as insulin and leptin are slower (tonic) in response. Large portions of the scientific evidence supporting similarities between the two areas are based in neuroimaging in humans and rodents. This review describes imaging modalities and common findings using noninvasive translational neuroimaging in both areas and in both humans and rodents.

Functional MRI (fMRI) offers anatomical and temporal specificity and allows measurement in blood flow changes in distinct areas of the brain. Advantages include noninvasiveness although imaging conscious animals requires specialized restraint devices and prolonged training. Currently, fMRI experiments in animal models of obesity have not been done. Due to the motionless requirements, experiments involving drug administration have been limited to the pharmacological effects of drugs on the brain in the anesthetized state. fMRI has been used to how a decrease in the dorsal and ventral striatum, thalamus and hypothalamus in response to heroin with a tolerance effect in those areas in response to the drug. fMRI in rodents have shown that cocaine increases activation in the frontal cortical regions, dorsal and ventral striatum and the thalamus and D1 (dopamine) receptor antagonism was able to block the cocaine induced brain response.

Positron emission tomography (PET) utilizes radiotracers and quantification of the tracer uptake in tissues. PET imaging allows for monitoring short and long term (multiple sessions) in the same subject. Newer technology allows scanning without immobilization. However, unlike fMRI, PET has low temporal resolution and radiotracer uptake rate and binding can be nonspecific. microPET has been used to study pharmacological effects of a drug on brain activity by measuring brain glucose metabolism with awake and unrestrained animals. For obesity, PET has been used to show greater metabolism in areas of the brain associated with sensory processing when no food is present. Also, obesity has been shown to be associated with impaired sensory sensitivity to interoceptive and exteroceptive stimuli. Finally, brain regions activated by an implantable gastric stimulator are also activated by drug cravings in addicted subjects.

QUESTIONS

1. T/F: Positron emission tomography can be used more reliably on conscious animals with a better temporal resolution.

2. Which group of homeostatic mechanisms is rapid in response?

a. Cholecystokinin, ghrelin and leptin

b. Glucagon-like peptide 1 and insulin

c. Ghrelin, cholecystokinin, and gastrin-releasing peptide

d. Insulin, leptin, ghrelin

3. Indicate which imaging modality fits with each statement below by writing (1) for fMRI or (2) for PET next to the statement:

a. Utilizes radiotracers

b. Anatomical specificity

c. To the authors knowledge, has not been used for obesity imaging in animal models

d. Uptake rate and binding of tracer can be nonspecific

ANSWERS

* 1. F. Temporal resolution is lower with PET)
  2. c
  3. a - 2; b - 1; c - 1; d - 2

**Hughes-Moore. IACUC Considerations Specific to the Use of Animal Models in Studies on the Neurobiology of Addictive Behaviors, pp. 68-71**

SUMMARY: The article aims to provide brief guidance to institutional animal care and use committee (IACUC) members for the review of addictive and neurobiological behavior research (ANBR) protocols involving animal models, especially rodent ones. Following a number of leads taken from the 2011 Guide for the Care and Use of Laboratory Animals, the author gives pointers under the following headings:

1. Rationale & Purpose of Proposed Use of Animals (need for clarity)

2. Clear, Concise Description of Procedures (sequential steps from point of acquisition to euthanasia or animal disposition)

3. Availability or Appropriateness of Less Invasive Procedures (administration of the substance of abuse and behavioral assessment may result in stress/distress; researchers need to consider the 3Rs)

4. Housing and Husbandry Requirements (very important to define housing, enrichment and all other aspects of husbandry and environment as there is ample evidence for these factors affecting behavioral outcomes; examples are given in the text)

5. Impact of Proposed Procedures on Animals' Well-Being (dysphoria and distress seen in humans with addictions may be seen as discomfort and distress in animals; danger of overdosing and of withdrawal syndrome; look out for irritability, changes in body temperature, weight loss, tremors, convulsions; appropriate monitoring and interventions)

6. Postprocedural Care and Observation (because there can be complications resulting from drug administration, withdrawal or behavior testing)

7. Description and Rationale for Anticipated or Selected Endpoints (need to have clear criteria for monitoring frequency and intervention to treat or cull so as to minimize stress/distress; based on sound knowledge of the potential deleterious effects of substances of abuse and the stressors involved in behavior testing and assessment)

8. Criteria and Process for Timely Intervention (a weighted assessment tool can be useful, carefully balancing the relative weight of standard criteria for intervention; these criteria may include cessation of grooming, abnormal or evoked vocalization, decreased activity, changes in sleeping/eating/eliminating patterns, restlessness, reluctance to move or sitting in a corner away from others, abnormal locomotion, hyperactivity or circling, abnormal posture, change in temperament or novel behavior)

9. Use of Hazardous Materials and Provision of a Safe Working Environment (additional risks posed by changes in animal behavior and also access and possible exposure of personnel to substances of abuse and specialized equipment; training paramount)

QUESTIONS

1. In the context of animal research, what does the acronym ANBR mean?

a. Association for Neurobiological Research

b. American National Board for Research

c. Animal Network for Biological Research

d. Addictive and Neurobiological Behavior Research

2. What could be described as common to all studies of addiction in animals?

a. The use of modern imaging modalities

b. Single-housing

c. Administration of substance of abuse and behavior assessment

d. Induction of abnormal behaviors

3. When considering the welfare (well-being) impact of the administration of addictive drugs to animals, which two factors should the researcher bear especially in mind?

a. Potential for overdosing and withdrawal syndrome

b. Irritation at site of administration and anaphylaxis

c. Toxic reactions and placebo effect

d. Sterility and solubility of compound

ANSWERS

1. d. Addictive and Neurobiological Behavior Research

2. c. Administration of substance of abuse and behavior assessment

3. a. Potential for overdosing and withdrawal syndrome