**ILAR J**

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***Animal Models of Drug Addictions: High Hopes for Therapeutic Treatments***

**Frascella et al. Introduction: Animal Models of Drug Addiction in Support of Novel Therapeutic Strategies, pp. 233-238**

Domain 3: research; Task K3: animal models

SUMMARY: Addictions to substances including alcohol, nicotine, marijuana and cocaine present important public health concerns.  This introductory article gives an overview of animal models.  "Substance addiction is a chronic relapsing brain disorder that results in the addicted individual's inability to limit drug consumption despite detrimental  
consequences (Meyer 1996).  Addiction research focuses on several efforts including induced neuroadaptations in the reward brain system, determining individual differences in behavior or neurobiology that promote addictive behavior, and identification of pharmacological targets for treatment.

Animal models of alcohol addiction have been valuable in determining molecular basis of many alcohol related behaviors that would have been difficult to determine from human studies.  There is controversy about the animal models used for nicotine addiction and further research is necessary to determine the translational value of animal models. Marijuana (Cannabis sativa) is the most widely used illicit drug by teenagers and adults.  The primary psychoactive component is THC.  Other related compounds can bind and activate the 2 types of cannabinoid receptors.  Animal models evaluate potential therapies to treat marijuana dependence and withdrawal.   Cocaine addiction has 3 hallmarks; 1. gradually escalating cocaine use, 2. escalating drug seeking despite adverse consequences and 3. increased susceptibility to stress- and drug-primed craving.  Animals exposed to extended access developed working memory deficits.  The authors state that the rat is the most frequently used animal species in drug addiction research.

Opiate addiction research includes molecular approaches, clinical issues and investigation into the contributions of NMDA receptor systems processes.  The opioid systems of the newborn are functionally different from that of the human adult.  Infants can develop opioid dependence. Methamphetamine causes a "persistent neurotoxic assault on the brain's dopamine neuronal system...".  The NIH National Institute on Drug Abuse, DEA and White House Office of National Drug Control Policy classify methamphetamine abuse as an epidemic.  Models include neurotoxicity and dopaminergic systems.   Finally animal research on ketamine may lead to improved animal models of schizophrenia.

QUESTIONS:

1. The most frequently used animal in addiction studies is \_\_\_\_\_\_.

2.  There are \_\_\_ types of cannabinoid receptors.

3.  Human infants can develop symptoms of opiate withdrawal.  T/F.

4.  Addicted individuals are unable to limit substance intake despite detrimental consequences.  T/F

ANSWERS:

1.  The rat.

2.  2 types.

3.  T

4. T

**Hopf et al. Translational Models of Interactions between Stress and Alcohol Consumption: Strengths and Limitations, pp. 239-250**

**Domain 3:** Research

**T1.** Facilitate or provide research support

**T2.** Advise and consult with investigators on matters related to their research

**T3.** Design and conduct research

**K6.** Characterization of animal models

**SUMMARY:** The article analizes the coplexity and significance of alcoholism and effective modeling of it in animals, with particulat focus on compulsive alcohol consumption, relationship between stress and alcohol intake, cross sesitization of stress and alcohol exposure, targeting stress in therapeutic intervention, neuroadaptation and genetic factors and challenges and inconsistencies inherent in both human and animal studies of alcoholism.

Suitability of animal models are usualy for binge drinking and some aspects of poor decision making, in these to aspects of alcohol consumption rodents are an effective model. Rodents can also be effectively used as models for stress related neuroadaptations. Rodent models of binge drinking are: limited access operant condition in rats, excessive drinking in dependent rats and mice, scheduled high access and "drinking in the dark" in mice. For poor decision making two models are poor response inibition and poor delayed discounting. Animal models allow experimental controll ove exposure to stress and alcohol and variables like age and sex.

Limits of animal models are compulsive behavior, particularly alcohol seeking despite aversive consequences. It is not clear that animal models can ever accurately capture the poor decision making inherent in denial and self delusion that an alcoholic uses to justify continued intake.

Adversion resistence during compulsive intake is defined as continuing to seek and consume alcohol despite adverse consequences. Some rodent models of this aspect of addiction are cocaine intake despite pairing with footshock (but similar experiment have not been reported with alcohol), quinine-resistent alcohol intake with intermittent access to alcohol (IAA) and continous access to alcohol (CAA), four bottle chioce paradigm, and alcohol deprivation effect (ADE).

Exposure to stressors may play a role in promoting alcohol intake. Most studies in humans have examined the relationship between acute exposure to stressors and alcohol consumption and, although a correlation between the two is not certain, the general concept that stress can promote alcohol drinkin in alcoholics is considered valid. Rodent models for stress and alcohol intake are usually models of relapse. Examples are ADE and reinstatement after extinction. Used stressors in these models are administration of yohimbine, foot shock, social defeat and restraint.

Stress and alcohol cross sensitization are another important aspect of alcoholism and other drugs addictions. Stress exposure during adolescence can enhance subsequent development of addictive behaviors. The ability of stress to facilitate human addictions may involve the interaction of genetic vulnerability and exposure to stress. These gene-stressor-alcohol interaction likely affects future pathological behavior through the development of neuroadaptations. One of these neuroadaptation is cross sensitization which involves likely protracted functional changes in one or more molecules in the brain. One of these molecules is cortisol (with the concomitant HPA axis). Literature suggests that humans with addictions exhibit elevated basal cortisol level but lower neurohormonal response to stress and that the stress regulatory system may undergo multiple functional changes in relation to stress and/or alcohol exposure. HPA and cortisol function has also been shown to affect alcohol self administration in rats. Corticotrophin-Releasing hormone is also another molecule involved in this mechanism. In monkeys has been demostrated that polymorphism of CRH promoter increases CRH levels and behaviral responses to stress and the likelihood that early life stress will lead to greater alcohol consumption. Also CRH1 receptor polymorphism has been associated with similar consequences in alcohol preferring rats. Striatal Dopamine (D2) Receptor  is also another important molecule. Lower D2 receptor levels in rats for exemple predict greater impulsivity and a higher level of drug intake.

On the therapeutic front of alcholism one largely unexplored option for modeling the ability to learn positive coping mechanism is to give alcohol experienced animal a choice between intoxicant and a conditioned safety signal or other positive experience. Also rodent and primate studies have shown that social interaction can buffer stress related development of addiction, although there are some caveats to this since some types of social interactions and social position may enhance alcohol consumption. Targeting adolescents in teaching buffering of shame, anger and stress in general may be also beneficial in preventing development of alcoholism later in life.

Finally further research is necessary to determine if animal models can be developed for more coplex aspects of human addiction such as self delusion or development of coping strategies to increase tollerance to stress.

**QUESTIONS:**

1. Which of the following is a rodent model for binge drinking:

a. Limited access operant condition in rats

b. Excessive drinking in dependent rats and mice

c. Scheduled high access

d. “Drinking in the dark" in mice

e. All of the above

2. It is not clear that animal models can ever accurately capture the poor decision making inherent in denial and self delusion that an alcoholic uses to justify continued intake.

a. True

b. False

3. Alcohol preferring rat is an inbred rat developed at Indiana University for high-alcohol-preferring behavior through bidirectional selective breeding of Wistar rats. These have high voluntary oral consumption of alcohol which leads to high blood alcohol. The P line of rat, as it is referred to, prefers an EtOH solution over water at least at 2:1 ratio. These rat lines also demonstrate distinct physiological and behavioral phenotypes in response to alcohol.

a. True

b. False

**ANSWERS:**

1. e

2. a

3. a

**Sobrian and Holson. Effects of Pre- and Neonatal Nicotine Exposure in Rodents: Inconsistent Evidence, pp. 251-294**

Domain 3: Research; K6.Characterization of animal models (e.g., phenotyping, behavioral assessment)

Primary Species: Mouse (Mus musculus) and Rat (Rattus norvegicus)

SUMMARY: This review article presents an analysis of the literature on behavioral effects of developmental exposure to nicotine, as assessed in rodent models that mimic the consequences for human offspring of maternal cigarette smoking.

* Analysis of a number of variables (e.g., physical, behavioral, and cognitive) shows that fetalexposure to nicotine does not consistently cause growth retardation or decreased birth weight, nor reliably affect motor activity.
* Combined pre- and neonatal rodent nicotine exposure is likely to result in delayed reflex development, global impairments in learning and memory, and an increased incidence of symptoms that model psychiatric illness.
* Determination of the consequences of human maternal smoking is hampered by a high level of confounding.
* The question of causation can only be resolved by eliminating or controlling the confounding variables & determining actual mechanisms of reported smoking-induced outcomes.
* Animal studies allow accurate measurement of the characteristics of the nicotine exposure, control of the dose & window of developmental exposure, with detailed evaluation of the effects of early exposure.
* The shorter lifespan of most experimental animals permits assessment of long-term consequences of developmental nicotine exposure & the persistence of these effects thru out the life span of the animal.
* Animal models provide a conceptual framework for understanding the mechanisms underlying nicotine-induced pathophysiology & suggest a casual relationship between developmental nicotine exposure and structural & functional impairments seen in the central nervous system.
* Prenatal exposure to nicotine during gestation day 21 to 22 ½ in rats mirrors tobacco exposure equivalent to that received in the first 2 trimesters of human gestation.
* In rats, postnatal maternal separation can produce lasting increases in anxiety-like behaviors, including exaggerated responses to pyschostimulant, voluntary alcohol consumption, stressor reactivity and changes in the brain neurotransmitter system.
* To model the 3rd trimester of human growth, rat pups must be exposed to nicotine post-natally, up thru post natal day 9 or 10 because this is the period of the rapid ‘brain growth spurt’ in the rat.
* Osmotic mini-pump placement for nicotine dosing allows consistency between animals regarding nicotine plasma levels and provides a linear correlation between the route of nicotine delivered & the plasma levels of nicotine.
* Rodent maternal plasma levels produced by gestational exposure to nicotine by several routes of administration are generally higher than those reported in humans during pregnancy.  Daily doses of rat maternal nicotine plasma levels at or below 2 mg/kg have been found to produce neurobehavioral changes in the offspring’s CNS.
* Rodent birth weight represents an accurate index of prenatal development.
* Route & developmental window of nicotine administration are the 2 variables that appear to contribute most to the disparate results reported for the effects of nicotine on rodent offspring birth & body weight.
* Animal models have provided direct evidence that prenatal nicotine exposure results in small cognitive impairments that may be related to attention deficits.
* The reviewed animal studies show that the combined pre-/neonatal nicotine exposure developmental window is the best translational model for determining the casual relation & mechanism responsible for the increased occurrence of psychiatric disorders after nicotine exposure.
* Animal studies have shown that nicotine exposure early in rodent development reduces the number of nerve cells and reduces brain weight.  Neuronal cell death in rodents after early nicotine exposure is seen by reduced dendritic arborization and cell size, increase mitotic figures and pyknotic cells.
* Despite extensive clinical and experimental literature, no consistent phenotype has emerged as a result of gestational or developmental exposure to either cigarette smoke or nicotine in rodents.
* One explanation for the lack of consistency in the effects of developmental exposure to nicotine in animals is that the typical animal experiment lacks the statistical power to reliably detect many of the effects seen in humans.

QUESTIONS:

* 1. The first 6 to 12 postnatal days of life in the rat are comparable to what stage of human gestation?

a. First trimester of human gestation

b. Second trimester of human gestation

c. Third trimester of human gestation

d. Not comparable to any stages of human gestation

2. Animal exposure to nicotine by the  \_\_\_\_\_\_\_\_\_\_\_\_\_\_ route  provides a slow, chronic release of nicotine that results in a steady state plasma concentration similar to those achieved in humans.

a. Subcutaneous injection

b. Oral gavage

c. Osmotic mini-pump

d. Inhalation

3. \_\_\_\_\_\_\_\_\_\_\_\_\_\_ is the main stimulant & addictive alkaloid in tobacco that has been implicated as a causative factor in the intrauterine growth retardation associated with smoking during pregnancy in humans.

a. Tar

b. Cyanide

c. Red dye #6

d. Nicotine

4. Which of the following tasks is NOT a task used to measure sensorimotor function in rats?

a. Swimming

b. Forepaw grip time

c. Beam walking

d. Conditioned avoidance response

5. Which of the following explanations is offered by the authors for the failure of rodent studies to duplicate effects of gestational cigarette smoke in humans?

a. Traditional sample sizes in rodent experiments are inadequate for reliably detecting prenatal nicotine effects.

b. Rodent studies lack standardized measures to compare data between studies for rodent gestational nicotine exposure.

c. Rodents are not affected by nicotine exposure.

d. Current rodent animal models of gestational nicotine exposure parallel human findings.

ANSWERS:

1. c

2. c

3. d

4. d

5. a

**Ramesh et al. Marijuana Dependence: Not Just Smoke and Mirrors, pp. 295-308**

SUMMARY:*Cannabis sativa* (marijuana) is the most commonly used illicit drug worldwide. Delta-9-tetrahydrocannabinol or Δ9-THC (THC) can lead to physical dependence in a number of species and alterations in behavioral, physiological, and biochemical responses. Withdrawal responses can include anger, aggression, irritability, anxiety, nervousness, decreased appetite or weight loss, restlessness, insomnia, and strange dreams. There appears to be a delay in expression of withdrawal symptoms most likely associated with the long half-life and other pharmacokinetics of THC. Because of this lack of contiguity between the discontinuation of the drug and onset of withdrawal responses, the latter has not been recognized as a clinically relevant syndrome.

The authors describe the preclinical and clinical research that supports the existence of a cannabinoid withdrawal syndrome. They also review the research evaluating potential pharmacotherapies to reduce cannabis withdrawal symptoms and examine the expanded knowledge about the regulatory mechanisms in the endocannabinoid system that may lead to promising drug targets.

The statistics for marijuana use over the last 30 years are staggering—42% of 18-yr-olds and 82% of 50-yr-olds report lifetime use—yet only one guidebook for medical professionals (*International Statistical Classification of Diseases and Related Health Problems*) recognizes a withdrawal syndrome as a component  of a cannabis dependence disorder.

Studies have shown that THC and many other cannabinoids bind to and activate two types of cannabinoid receptors which are heterogeneously expressed throughout the central nervous system and periphery. Additional studies showed the symptoms associated with marijuana abstinence which include impaired performance on a task measuring attention and with chronic use (which often happens when withdrawal symptoms increase)deficits associated with complex decision making and cognitive planning are seen. However, withdrawal symptoms do not appear to predict relapse after 2 or more years of abstinence.

The development of cannabinoid receptor antagonists (rimonabant) has been very useful in studies of precipitated withdrawal in cannabinoid dependent animals. Rimonabant binds with high affinity to the cannabinoid receptor and antagonizes the pharmacological effects of many cannabinoid receptor agonist activities in both laboratory animals and humans. Rimonabant challenge to THC-dependent mice led to less time in the open-arm component of the elevated plus maze test, suggesting an anxiogenic-like effect in subjects undergoing cannabinoid withdrawal, but failed to elicit aversive or dysphoric effects in the conditioned place avoidance test. Other treatment strategies are mentioned, such as fatty acid amide hydrolase (FAAH) inhibitors—URB597 and PF 3845—which in the former, did not produce rewarding effects in the rat conditioned place preference pardigm, did not substitute for THC in drug discrimination paradigm, and is not self-administered by nonhuman primates. The other FAAH inhibitor (PF 3845) did not lead to desensitization or downregulation of  cannabinoid receptor-mediated synaptic plasticity of hippocampal neurons. Another treatment target, monoacylglycerol lipase (MAGL—JZL 184), in contrast, led to mild cannabinoid withdrawal signs after rimonabant administration, as well as regionally dependent changes in cannabinoid receptor downregulation and desensitization in the brain and impaired endocannabinoid-mediated synaptic plasticity. JZL 184 did alleviate the intensity of the withdrawal signs.

The differential actions of prolonged FAAH and MAGL inhibition are not fully understood. Nonetheless, these studies provide proof of principle that bolstering endogenous anandamide through the inhibition of their catabolic enzymes may be viable approaches to reduce cannabis withdrawal symptoms. Other treatment strategies include dronabinol (oral THC), lofexidine (an alpha-2-adrenergic receptor agonist), nefazodone (an antidepressant), atomoxetine (a norepinephrine reuptake inhibitor indicated for attention deficit hyperactivity disorder), divalproex (a mood stabilizer), lithium, and quetiapine (an atypical antipsychotic) and bupropion (commonly used drug for treating tobacco addiction) which showed a worsening of signs. The failure of bupropion to treat marijuana withdrawal underscores the need to treat cannabinoid withdrawal as a unique syndrome and not simply as another form of smoking cessation.

QUESTIONS:

1. What is the most commonly used screen for novel anxiolytics, as well as a probe for anxiety in transgenic mice?

2. High levels of anxiety is correlated with more time spent in which part of the elevated plus maze test—open or closed?

3. What is another commonly used test for measuring anxiety in rodents?

ANSWERS:

1. The elevated plus maze.

2. The closed arm.

3. The light-dark exploration test.

**Ahmed and Kenny. Cracking the Molecular Code of Cocaine Addiction, pp. 309-320**

Primary Species: Rats

Domain 3: Research, Task 2: Advise and consult with investigators on matters related to their research

**Summary:**

Introduction

Animal models are a reverse addiction – seek to make drug naïve subjects dependent on or addicted to cocaine; rats are the most commonly used species in this type of research

Goal = increased understanding of the neurobiology of cocaine addiction to develop better treatment options

Difficult to validate if rats are truly addicted to cocaine

Medical definition of addiction = self administer cocaine and display behaviors consistent with humans (escalation of cocaine intake, continued use despite negative consequences)

Making Animals Addicted to Cocaine

Groups self-administer cocaine IV for days - weeks

Control rats – limited access (1 hour/day)

Experimental rats – extended access (≥ 6 hours/day)

Rats with extended access develop behavioral and neurobiological changes not seen in the control rats (limited access)

Hallmark signs = escalation of drug use, difficulty abstaining from drug seeking

Gradually increased total and hourly intake

Work harder to access drug (higher breakpoint = maximum effort that rats accept before they stop responding to the drug)

Seek drug even in the presence of a danger signal

Long incubation period required before drug seeking increases (may be due to loss of early withdrawal effects that interfere with drug seekinginitially)

Sensitivity to stress and cocaine primed reinstatement is greater

Decreased working memory, recognition memory, visual attention, and motor impulsivity

When given a choice between cocaine and nondrug option the majority chose the non-drug option even after extended cocaine use.  May indicate that most rats (and humans) are resistant to addiction

Molecular Mechanisms That Regulate Vulnerability to Cocaine Addiction

MicroRNAs

Dorsal striatum – key brain region altered in cocaine-addicted humans

miR-212 upregulated in dorsal striatum of rats with extended access (not limited or extended but passive exposure)

miR-212 overexpressing rats decreased intake (protective mechanism when levels are higher than physiological normal)

Methyl CpG Binding Protein 2 (MeCP2)

Expression is higher in the dorsal striatum of rats after repeated cocaine exposure

Decreasing it in the dorsal striatum blocked cocaine intake escalation and lead to a decline in intake

miR-212 inhibits MeCP2 expression 🡪 decreased cocaine-taking behavior

Brain-Derived Neurotrophic Factor (BDNF)

MeCP2 levels closely correlate with BDNF

Increases 🡪 enhanced sensitivity to psychomotor stimulant effects and loss of control over intake with overexpression as well as similar behavioral effects to addicted humans (e.g. weight loss, agitation, repetitive face scratching leading to trauma)

Decreases 🡪 decreased cocaine self-administration

Lead to increases in midbrain dopamine and amygdala neurons 🡪 cause of craving during prolonged abstinence

Conclusions

MiR-212, MeCP2, and BDNF function together in rats with extended access to cocaine (can lead to or protect from addiction depending on their levels)

miR-212 Future Research

Effects on drug and stress primed craving

Effects on cognitive deficits

Effects on addiction to other drugs

**Questions:**

What is the function of microRNAs (miRNAs)?

What is the function of methyl CPG Binding Protein 2 (MeCP2)?

Name two other drugs, mentioned in this article, which may have similar addiction patterns to cocaine.

Name one drug, mentioned in this article, which with repeated access does not lead to escalation of use.

**Answers:**

Small nonprotein-coding RNAs that regulate gene expression at the posttranscriptional level.  They bind to complementary sequences, known as miRNA response elements, in the 3’ untranslated region of target mRNA transcripts.  They can facilitate transcript degradation and/or inhibit translation.  Highly pleiotropic and may be able to control many genes but some may be spatially restricted.

Binds to methylated DNA to recruit histone deacetylases and other transcriptionalrepressors to silence target genes.  Has been shown to be a key regulator of many aspects of neuronal plasticity.

Methamphetamine and heroin

Nicotine (reasons are unclear but it may be due to the unpleasant side effects that result from high doses)

**Reti et al. Mediating the Effects of Drug Abuse: The Role of Narp in Synaptic Plasticity, pp. 321-328**

Reviewer: Amanda Fisher

Title: Mediating the effects of drug abuse: the role of Narp in synaptic plasticity

Authors: IM Reti, AM Blouin, PF Worley, PC Holland, AW Johnson, JM Baraban

Domain 1 T2

Species: Narp KO mice and Narp WT mice

Summary: Drug addiction induces structural changes in dendritic spines along with long-term depression (LTD) and long-term potentiation (LTP) in reward circuits. There is interest in determining whether similar signaling pathways mediate physiological forms of plasticity and long lasting changes induced by addiction. Narp (neuronal activity-regulated pentraxin) is a protein induced in LTP and has been implicated in mediating enduring forms of synaptic plasticity. Pentetraxins form pentameric structures that aggregate into larger complexes. Narp also has prominent constitutive expression in many brain pathways and is expressed in heterogeneous fashion. Narp is found in the serum and levels are elevated in response to same stressors that trigger vasopressin secretion. Serum Narp originates from the posterior pituitary. Narp modulates acquisition and extinction of aversive responses to morphine withdrawal and may regulate plasticity processes that underlie drug addiction. Narp KO mice were compared with Narp WT mice and results indicated that KO mice were unable to process altered reward information (the pretrial devaluation of a food reward did not alter their behavior suggesting that they are unable to recalibrate the appetitive value of the reward). During repeated tests in the absence of morphine injections (extinction studies: the process by which a previously established stimulus relationship is broken, causing a reduction in responding), WT mice showed return to preconditioning levels while KO mice did not. It is suggested that Narp regulates plasticity in the major afferent pathways to the nucleus accumbens. And behaviorally, Narp KO mice reveal a selective defect in extinction studies and may be useful in research on mechanisms of extinction from drug craving.

Questions:

1.       What is Narp?

2.       Where does serum Narp originate from?

3.       What are extinction studies?

Answers:

1.       Narp (neuronal activity-regulated pentraxin )is a protein induced in long-term potentiation

2.       Serum Narp originates from the posterior pituitary

3.       Extinction studies are done using the process where a previously established stimulus relationship is broken causing a reduction in responding.

**Barr et al. Changing Mechanisms of Opiate Tolerance and Withdrawal during Early Development: Animal Models of the Human Experience, pp. 329-341**

SUMMARY: In this review the authors focused on the study of tolerance and withdrawal after repeated or acute exposure of infants to opiates (mostly morphine) to identify the mechanisms that are similar to and different from those understood  in adults.

Numerous studies have shown that human and not human infants become tolerant to the analgesic effects of opiates but there are no data  suggesting that the age of the human infant influences the magnitude or rapidity of tolerance to opiates. Indeed, tolerance in the infant rat is tipically of a lesser degree than that of the older pup or adult rat.

Opiate withdrawal in human or nonhuman adults includes activation of the sympathetic nervous system but in the infant these processes are immature; thus classic signs in the adult rodent, such as teeth chattering, jumping, diarrhea, “wet-dog shakes” and ptosis do not occur between 14 and 21 days of age in the rat.

There are multiple possible reasons for different withdrawal syndromes in the neonate and the adult.  Given the immaturity of the central nervous system (CNS) in the infant, it is likely that the neural mechanisms differ among infants and adults. The anatomical circuits are at least similar and the opioid receptor involved is the same. In contrast, the role of intracellular signals, in particular those related to glutamate N-methyl-D-aspartate (NMDA) receptors, appears to differ.

There are few studies of the involvement in early development of substance P, acetylcholine and endothelins in either tolerance or withdrawal to opiates so their role remains to be clarified.

Further research in all these areas will enhance understanding of the mechanisms underlying opiate-induced neural changes.

QUESTIONS: true or false

1. In therms of overall rates of protein synthesis in the brain, the rat is altricial and at birth is roughly equivalent to an early-third-trimester human fetus, or in other words, this places the rat at about 18 days of postnatal age when the human is born.
2. Tolerance is defined as a decreased response to a drug after administration of or exposure to the drug; empirically it is defined as a shift to the left in the dose-response curve with a decreased effective dose (ED50) or effective concentration (EC50).
3. Tachyphylaxis or acute tolerance can occur both after multiple administrations and after a single injection.
4. Physical signs of opiate withdrawal in human and non human adults include flulike symptoms such as muscle aches, runny nose, abdominal pain and diarrhea, dilated pupils, and nausea and vomiting.
5. In young pups (less than a week old) kappa opioid receptors are the major receptor type involved in withdrawal.
6. The hypothalamus mediates the aversive properties of opiate withdrawal in the adult.

ANSWERS:

1. True
2. False. It is defined as a shift to the right and an increased effective dose (ED50) or effective concentration (EC50).
3. True
4. True
5. False. Mu opioid receptors are the major receptor type involved in withdrawal in young pups.
6. False. The amygdala mediates the aversive properties of opiates withdrawal in the adult.

**Glass. Opioid Dependence and NMDA Receptors, pp. 342-351**

Domain 2: Management of Pain and Distress

SUMMARY: The process of opioid dependence is distributed across a highly complex network of sensory, limbic, and memory systems that regulate homeostasis and is frequently associated with glutamate-dependent synaptic plasticity.  Animal models have been instrumental in understanding the role of NMDA-type glutamate receptors in opioid dependence behaviors, including opioid withdrawal response, learned contextual aversion, and the extinction of conditioned aversive responses. The involvement of NMDA receptors in opioid rewards suggests that manipulating their function may be beneficial in managing opioid addiction pharmacologically.

QUESTIONS:

1. What is the scientific name of opium poppy?
   1. *Lachryma papaveris*
   2. *Papaver somnifereum*
   3. *Eschscholzia californica*
   4. *Meconopsis cambric*
2. T or F. Morphine’s major acute biological effects are mediated by activation of the µOR.

ANSWERS:

1. B
2. T

**Kuhn et al. Nucleus Accumbens Invulnerability to Methamphetamine Neurotoxicity, pp. 352-365**

Reviewer: Corinna Kashuba, [ckashuba@niu.edu](mailto:ckashuba@niu.edu)

Title: Nucleus Accumbens Invulnerability to Methamphetamine Neurotoxicity

Authors: D.M. Kuhn, M. Angoa-Perez, and D.M. Thomas

Domain 3, Task 2

Species: Review of similar research findings in multiple primary species (primates, rodents)

Summary:

This review summarizes the salient features of Methamphetamine (Meth)-induced neurotoxicity with a focus on the dopamine neuronal system. Methamphetamine is a member of the amphetamine family of psychostimulant drugs. The consequences of Meth-induced neurotoxicity manifest as persistent depletions of dopamine, inhibition of tyrosine hydroxylase, inactivation of the dopamine transporter, reduction in function of the vesicle monoamine transporter, degeneration of fine, unmyelinated axons, and apoptosis in humans and in animal models.

Role of Non-neuronal cells in methamphetamine neurotoxicity:

Microglia - activated by Meth, produce virtually all reactants that are essential for the toxicity associated with neurotoxic amphetamines, but the question still remains as to whether they cause nerve ending damage related to Meth or if they just react to it.

Astrocytes - changes in astrocyte expression of glial fibrillary acidic protein have been used very effectively as an index of Meth-induced neurotoxicity. The exact role of astrocytes in Meth-induced neurotoxicity is unknown but astrocytes could possibly mediate glutamate release and uptake in brain areas showing damage after Meth intoxication.

Neuronal, Microglial, and Astrocyte Cross-talk and Meth Toxicity - Meth might cause neurotoxicity via different mechanisms depending on the balance of drug-induced communication among nerve terminals, microglia, and astrocytes and the resulting production of reactive oxygen species, reactive nitrogen species, inflammatory and excitatory species, and neurotrophic factors.

Brain-region Specificity of Meth Neurotoxicity:

Dopamine nerve endings in the caudate-putamen are damaged by Meth in a highly delimited manner. The nucleus accumbens is largely spared the damage that accompanies binge Meth intoxication, but relatively subtle changes in the disposition of dopamine in its nerve endings can lead to dramatic increases in Meth-induced toxicity in the caudate putamen and overcome the normal resistance of the nucleus accumbens to damage.

There are differences between mice and rats in the sensitivity of the nucleus accumbens to Meth damage. Substantia nigra damage has varied over multiple species and studies. Meth induces inflammation, gliosis, and neurodegeneration in the hippocampus and cortex, resulting in learning and memory deficits.

Role of Dopamine, Serotonin, and Norepinephrine in Meth Neurotoxicity:

Meth causes a dramatic change in the homeostatic mechanisms that normally regulate dopamine, serotonin, and norepinephrine (altering their synthesis, storage, and release) and create additional neurotoxic species via reaction of the transmitters with reactive oxygen species and reactive nitrogen species generated locally by Meth.

Changes in Nucleus Accumbens in Response to Meth Neurotoxicity:

The nucleus accumbens is critical to reward mechanisms and decision making, and is important in Meth addiction and the reinstatement of Meth-seeking after withdrawal (the nucleus accumbens regulates impulsivity and response inhibition). It is highly resistant to Meth-induced neurotoxicity by comparison to the caudate putamen but even small changes in the disposition of dopamine in nerve terminals of the nucleus accumbens can increase the susceptibility of this structure to Meth-induced damage.

Conclusions:

Endogenous neurotransmitters can influence the course of Meth's damaging effects.

Non-neuronal cells seem to be important modulators of Meth neurotoxicity through their involvement in complex cross talk with dopamine nerve terminals soon after Meth intoxication.

Neurotrophic factors such as pleiotrophin may play a role in nucleus accumbens resistance to Meth neurotoxicity.

More than two decades of study using animal models of Meth-induced neurotoxicity have contributed to a much better understanding of both the nature of brain damage caused by Meth and the mechanisms underlying its neurotoxicity.

There are numerous parallel studies in human abusers that are based on studies using animal models, and these have resulted in growing interest in the development of prevention strategies, new pharmacotherapies for treating Meth addition, and restoring neuronal function in individuals with persistent behavioral and neuronal deficits.

Questions:

1. What is the mechanism of action of Meth by which it damages the dopamine neuronal system?

2. What group of drugs does Meth belong to?

3. What is the role of the nucleus accumbens in terms of human behavior/thought processes?

4. Which is more sensitive to damage from Meth: the caudate putamen or the nucleus accumbens?

Answers:

1. The mechanism of action of Meth is not fully understood.

Oxidative stress is a mediator, with a potential role for nitric oxide, superoxide dismutase, and peroxynitrite (a cytotoxicant formed by the reaction of nitric oxide and superoxide dismutase). Glutamate excitotoxicity has been implicated - mitochondrial dysfunction may be a final, common path by which nerve terminal function is diminished.

Hyperthermia is a dangerous outcome of acute Meth intoxication.

2. Meth belongs to the amphetamine family of psychostimulant drugs

3. The nucleus accumbens is critical to reward mechanisms and decision making, and is important in Meth addiction and the reinstatement of Meth-seeking after withdrawal. It regulates impulsivity and response inhibition.

4. The caudate putamen is more sensitive to damage from Meth than the nucleus accumbens.

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**Trujillo et al. The Neurobehavioral Pharmacology of Ketamine: Implications for Drug Abuse, Addiction, and Psychiatric Disorders, pp. 366-378**

Domain 2: Management of Pain and Distress; K5: Pharmacological interventions for pain and distress and their effects on physiology, including age and species differences for such interventions, and depth and duration of analgesia provided by such interventions

Domain 3: Research; K3: Animal models (spontaneous and induced) including normative biology relevant to the research (e.g., background lesions of common strains)

SUMMARY: Ketamine was developed in the early 1960s as an anesthetic and has been used for medical and veterinary procedures since then.  It is a potent anesthetic that does not produce respiratory depression at anesthetic doses which make it particularly useful for emergency situations.  It also has a rapid onset and predictable duration of action, some analgesic, anxiolytic and amnestic effects and mild effect on cardiovascular function make it a useful drug. Ketamine is an NMDA receptor antagonist.  Since central sensitization involves NMDA receptors, ketamine has been used in the treatment of certain types of pathological pain. The reigning explanation for the actions of ketamine is the hypoglutamatergic hypothesis: ketamine produces its effects by blocking the ability of glutamate to activate NMDA receptors.  However it has recently been suggested that the effects are via a hyperglutamatergic mechanism by increasing glutamate in certain brain areas and thereby produce some of the drug’s behavioral effects.  Ketamine has very rapid and long-lasting antidepressant effects when administered at subanesthetic doses.  Ketamine’s ability to produce both negative and positive symptoms of schizophrenia, as well as cognitive dysfunction have made it a model for schizophrenia.  Subanesthetic doses of ketamine produce locomotor stimulation accompanied by ataxia in rodents.  When administered with psychomotor stimulants ketamine produces potent locomotor depression. In rodent models, the ability of drugs to block the behavioral actions of ketamine is often used as a preclinical assay of antipsychotic effects. Early studies on repeated use of ketamine focused on changes induced by high doses and reported that tolerance developed to the anesthetic effect of the drug.  In the 80s and 90s there was a dramatic increase in the recreational use of ketamine.   Reward is considered to be an essential aspect of addiction to ketamine.  Two widely used and effective measures of reward in animal models involve self-administration and conditioned place preference.  Ketamine was reinforcing in a small but significant number of self-administration experiments.  Place conditioning produced by ketamine was statistically significant but typically less pronounced than that induced by other drugs in the studies.

QUESTIONS:

1. Describe a self-administration animal model.
2. Describe a conditioned place preference animal model.
3. NMDA receptors are ligand-gated cation channels that open in response to the binding of what molecule(s)?
4. Na+
5. K+
6. Glutamate
7. Glycine
8. c and d
9. What DEA schedule is ketamine?
10. What disorder is ketamine used to produce an animal model?

ANSWERS:

1. An animal performs a task to obtain a drug; an increase in the frequency of the task performance is an index of the reinforcing properties of the drug.
2. Uses a chamber with two compartments distinguished by different cues.  A test drug is reliably paired with one compartment and a placebo with the other.  If, after conditioning, the animal spends more time in the drug-associated environment, the drug is considered rewarding.
3. e
4. Schedule III
5. Schizophrenia

**Nicholson and Ator. IACUC Perspective on Drug Addiction Research, pp. 379-385**

SUMMARY: IACUCs have many legitimate concerns on protocols concerning addictive drugs.

Investigators may hold “Researcher” registrations with the FDA. They are legally approved to receive and use the controlled substances approved under their registrations. These individuals, not their institutions, are personally responsible for meeting state and federal laws.

Protocols in which psychoactive drugs are used should consider the adverse effects of the drugs as well as the potential for toxicity, the effects on food and water consumption, mobility, and sedation.

For animals on chronic exposure protocols, a monitoring plan should be in place for assessing behavior, appearance, elimination, food consumption, as well as a contingency plan for addressing adverse effects.

When a withdrawal syndrome is likely, the protocol should describe the withdrawal as well as the duration and any approaches to mitigate discomfort. For drugs known to produce withdrawal, tapering of the drug dose can prevent or reduce drug withdrawal effects at the termination of the study.

A comparison of the distribution of dopaminergic receptors in the frontal cortex and the hippocampus is the most similar among primates and different from rodents.

Pharmacokinetic studies in humans, monkeys, and rats have shown that monkeys provide the most qualitatively and quantitatively accurate predictions of human pharmacokinetic parameters compared with other species.

Protocols that use food regulation should include the following: justification for the levels and duration of restriction, a description of how the restriction will be arranged and whether individual housing in required, and a plan for monitoring body weights.

Investigators using stressors should include: justification for using the stressors, duration of the stress exposure, plans for monitoring animal health, and a description of the procedure to ensure that the equipment generates the appropriate shock intensity.

QUESTIONS:

1. T/F Institutions are responsible for the drugs an investigator with a Researcher registration has on that registration.

2. A comparison of the distribution of dopaminergic receptors in which areas of the brain is the most similar among primates and different from rodents.

a. Hypothalamus and hippocampus

b. Frontal cortex and hippocampus

c. Nucleus accumbens and frontal cortex

d. Hippocampus and nucleus accumbens

3. Pharacokinetic studies in humans, monkeys, and rats have shown that \_\_\_\_\_\_\_\_\_\_ provide the most qualitatively and quantitatively accurate predictions of human pharmacokinetic parameters compared with other species.

ANSWERS:

1. False. Researchers are responsible for drugs on a Researcher registration.

2. b. Frontal cortex and hippocampus

3. Monkeys

**Tardif et al. Workshop Summary: Neotropical Primates in Biomedical Research, pp. 386-392**

ILAR Journal Volume 52, Number 3, 2011 Page 386~392

Workshop Summary: Neotropical Primates in Biomedical Research

Authors: Suzette D. Tardif, Christian R. Abee, and Keith G. Mansfield

Introduction:

A workshop on Neotropical Primates in Biomedical Research was sponsored by the National Center for Research Resources of the NIH and held in September 22~23, 2010. The goals of the workshop were to (1) review the use of neotropical primates in biomedical research, (2) identify areas where neotropical primates are required for research, (3) identify areas where neotropical primates facilitate research and (4) identify barriers or challenges to the continued use of the species as biomedical models.

Questions:

1. New World monkeys with the smaller size, faster maturation and shorter life span than Old World monkeys are efficient models and present unique opportunities for studying human health and disease. **Answer: T or F**
2. Old World monkeys are more distantly related to human (separation 37~52 million years ago) than the New World monkeys (separation 27~36 million years ago). **Answer: T or F**
3. The New world primates have the advantages of small monkey in terms of biosafety, requirement for less test material and substantial cost saving, all of which could accelerate validation in bioterrorism countermeasures. **Answer: T of F**
4. The Old World monkeys are good models to be infected with human malarial parasites compared with the New World monkeys. **Answer: T or F**
5. The common marmoset is the first animal model of persistent infection and pathogenesis with Kaposi’s sarcoma-associated herpesvirus (KSHV) that reliably reproduce important aspect of human infection. **Answer: T or F**
6. The squirrel monkey was one of the first primate species to demonstrate the Parkinsonian neurotoxic effects of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). **Answer: T or F**
7. What species of monkeys provide the best combination of prion transmission susceptibility? They have short and narrowly distributed incubation periods (25 +- 5 months) duration of illness (1.3 +- 1.6 months) **Answer: a)Owl monkeys, b) marmosets, c) squirrels**
8. What species of monkeys have large eye and globelike with a more spherical lens than that of diurnal monkeys, but unlike other nocturnal mammals they lack a tepetum lucidum. The retina contain smaller number of cones compared to other primates. **Answer: a)Owl monkeys, b) marmosets, c) squirrels**
9. Obese marmosets display many of the pathological conditions associated with obesity in humans; insulin resistant, diabetes, and most importantly, hyperlipidemia and associated hepatomegaly and lipid accumulation in the liver. **Answer: T or F**

Answers:

1) T;

2) F; New World monkeys are more distant

3) T;

4) F; New World monkeys are good model

5) T;

6) T;

7) C;

8) A;

9) T.

**Bayne et al. Harmonizing Veterinary Training and Qualifications in Laboratory Animal Medicine: A Global Perspective, pp. 393-403**

**Reviewer:** Giuseppe Dell'Anna [giuseppedellanna@gmail.com](mailto:giuseppedellanna@gmail.com)

Bayneet al. 2011. Harmonizing Veterinary Training and Qualifications in LaboratoryAnimal Medicine: A Global Perspective. ILAR J 52(3):393-403

**Title:** Harmonizing Veterinary Training and Qualifications in Laboratory Animal Medicine: A Global Perspective

**Authors:** Kathryn Bayne, David Bayvel, Judy MacArthur Clark, Gilles Demers, Christophe Joubert, Tsutomu Miki Kurosawa, Ekaterina Rivera, Ouajdi Souilem, and Patricia V. Turner

**Domain 6:** Education

**Task 1:** Provide education in academic and/or laboratory animal residency programs

**Task 2:** Outside of formal training programs, mentor those interested in or involved in laboratory animal medicine

**Summary:** Due to animal based research and education becoming more and more international and to the trend of outsourcing for a lot of pharmaceutical companies, the Authors analyze the  concerns about appropriate animal welfare standards, personnel qualifications, and the quality of the data generated from animals used in countries with limited animal welfare oversight.

The OIE in its Terrestrial Animal Health Code states that institutions using animals for research and teaching should have a veterinarian “with the necessary expertise to work with research animals, whose specific role is to provide advice on the care, use and welfare of such animals.” From this statement it can be concluded that the veterinarian assumes a primary role to provide that high quality veterinary care and animal welfare to the institution. ACLAM, ECLAM, JCLAM and KCLAM offer specialty board certification that are based on standards set by the umbrella organization IACLAM. In many other countries such training is not available. The OIE in its Terrestrial Animal Health Code states also that “veterinarians working in an animal research environment have veterinary medical knowledge and experience in the species used…….. Veterinary care includes responsibility for promoting an animal’s health and welfare………… The veterinarian should have authority and responsibility for making judgments concerning animal welfare. Veterinary advice and care should be available at all times”. There is large variability in guidance and oversight in most countries for standards of veterinary care for research institutions. In most cases those standards are originated by laboratory animal medicine professional organizations. Exceptions to this trend are USA (AWA and R), UK (Animals Act), Canada (provincial legislations) and the EU (Directive 2010/63/EU). In the USA ACLAM certification is desirable but not required, in the UK a training course during the first year in the position is required, in the EU “expertise” in the field is required, in India and Singapore state that the veterinarian should have training or experience in laboratory animal, in Japan there are no specific regulations for qualification of veterinarians in this field, finally Australia requires veterinarians to familiarize themselves with the biology and clinical characteristics of the species used. This diversity of guidance can result in tangible consequences for the animal and the research. Evidence of this variability has been demonstrated by data made available from AAALAC International. AAALAC recently reported that inadequacies in the program of veterinary care rank third highest in the Pacific Rim region.

Shared concern about the need to harmonize veterinary qualifications in laboratory animal medicine prompted a collaborative effort by the OIE, IACLAM, and US National Re- search Council’s Institute for Laboratory Animal Research (ILAR) to address this issue, with the following goals:

* identify core knowledge and practical skills necessary for the laboratory animal veterinarian;
* articulate methods for delivering appropriate training to veterinarians who wish to practice laboratory animal medicine;
* determine the breadth and detail of information to be provided to trainees;
* identify potential methods for assessing competency after training;
* evaluate means of ensuring accessibility and translation of relevant information in laboratory animal medicine and science; and
* assess the value of and methods to provide continuing education.

Three pivotal laboratory animal science meetings were held in separate geographic regions to evaluate the laboratory animal medical veterinary community perspective on veterinary qualifications and training in this field: the June 2010 FELASA meeting in Helsinki; the October 2010 meeting of the American Association for Laboratory Animal Science (AALAS) in Atlanta; and the November 2010 meeting of the Asian Federation of Laboratory Animal Science Associations in Taipei. Five key points were used to determine the knowledge and the skills necessary to develop proficient laboratory animal medicine veterinarians:

* Role of the veterinarian in laboratory animal science
* Core knowledge and practical skills
* Educational approaches
* Experience
* How much training

There are several key documents from different areas of the world regarding adequate veterinary care and the role of the veterinarian in a research institution. ACLAM will identify the following primary responsibilities:

* disease detection and surveillance, prevention, diagnosis, treatment, and resolution;
* guidance and monitoring in (1) handling and restraint of animals; (2) anesthetics, analgesics, and tranquilizers; and (3) methods of euthanasia;
* review and approval of all preoperative, surgical, and postoperative procedures;
* promotion and monitoring of animal well-being before, during, and after experimentation or testing; and
* involvement in the review and approval of all animal care and use at the institution.

And the following “ancillary” roles:

* providing training to staff in the care and use of laboratory animals,
* providing input to the occupational health and safety program
* monitoring for zoonotic diseases
* advising on standards of hygiene in the animal facility
* advising on and monitoring biohazard control policies and procedures

The FELASA/ECLAM/ESLAV guidelines identify the following key areas:

* assessment of animal welfare, including behavioral evaluation;
* early recognition of signs of pain and distress, and their alleviation;
* prevention, diagnosis, and treatment of disease;
* verification that animals procured for research are derived from a licensed source or approved breeder;
* implementation of an appropriate health monitoring program;
* appropriate record keeping;
* involvement in the training and assessment of competence of those who conduct procedures that may affect animal welfare;
* review of anesthetic procedures;
* consultation with the researcher about proposed surgical procedures and adequate perioperative care;
* advice, training, and oversight of euthanasia procedures;
* participation in the review of proposed research and implementation of the Three Rs

The OIE Terrestrial Animal Health Code has been recently revised to include the following responsibilities for veterinarians in the laboratory animal medicine:

     clinical duties, including preventive medicine, disease surveillance, diagnosis and management of disease, and management of controlled drugs;

     postmortem examinations;

     maintenance of veterinary medical records;

     advice on zoonotic risks and notifiable diseases,

     surgery and postoperative care,

     analgesia, anesthesia, euthanasia,

     humane endpoints.

There was also agreement among the participants to the meetings and discussion groups that the role of the veterinarian as a trainer in lab animal medicine and as figure involved in protocol review was very important.

As for the core competencies and skills the veterinarian should have the following were agreed to be relevant:

* Understanding of anatomy, physiology, pathology, and behavior of animals used in research and teaching;
* Be able to make, understand, and respond appropriately to clinical observations and collect samples to aid in the diagnosis of problems observed;
* Be able to recognize and mitigate animal pain and distress;
* Be skilled in the diagnostic method and able to interpret diagnostic information, including evaluation of the available health history of the animal;
* Be able to safely and humanely restrain animals;
* Be able to administer anesthesia and analgesia, understanding the most safe and efficacious agents to use for various laboratory animal species;
* Understand and implement aseptic technique for procedures, including surgery;
* Have basic surgical skills for common laboratory animals
* Being knowledgeable of ethical and bioethical issue
* Being familiar with the research methodology
* Knowledge about occupational health and safety, biosecurity practices, biology of and medical care for nontraditional species; available types of caging and support equipment; the potential impact of various facility environmental factors on both animal well-being and experimental data; basic management/supervisory techniques; and interpersonal skills

About approaches to deliver the training to laboratory animal veterinarians, there is formal and informal routes. For specialist training in laboratory animal medicine, ACLAM recognizes residency training programs must provide a minimum of 200 hours of didactic training and 2000 hours of applied training in addition to some research training, culminating in a first-author hypothesis-driven scientific manuscript in bio- medical research. ECLAM, JCLAM and KCLAM also follow a similar model for their residencies. Alternatives for veterinarians unable or unwilling to go through a residency program are distance certificate programs and mentoring programs, but even the two latter are very difficult to identify in developing countries. Given this lack of opportunities and consistency, the authors determined that a “ladder approach” to skill and knowledge development for veterinarians laboratory animal medicine. Premise of the ladder approach is that veterinarians hold a license or comparable certificate of qualification to practice general veterinary medicine in the country or region in which they are employed and then go on to enhance this fundamental education through various levels of training/support. Four levels of support where identified: (1) a mentor (either on- or off-site); (2) on-the- job experience supplemented with relevant continuing education; (3) a certificate, residency, diploma, or degree program in laboratory animal medicine; and (4) specialty board certification. Scope and scale of the program to be supported will be determining factors in selecting the more suitable training path. For consulting veterinarians the initial education and training plan may include an online course in elements of laboratory animal medicine within their first year of employment, a formal short course in elements of laboratory animal science in the second year, attendance at a conference or workshop specific to laboratory animal science of medicine at least once every 3 years, membership in a national or international professional laboratory animal medicine association, and a subscription to at least one journal in laboratory animal science. For institutional veterinarians the suggestions are participation in a formal educational or certificate program in laboratory animal medicine within the first year of employment, participation in at least one relevant workshop or conference within the first 3 years, participation in a laboratory animal science short course or practicum within the first 4 years, member- ship in a national or international professional laboratory animal medicine association, and subscriptions to relevant journals.

Assessment of competency can be either formative (e.g., gauging competency at new skills acquisition or the ability to critically assess animal use protocols) or summative (e.g., through a final test or examination). Formal academic programs enable such assessments. For less formal types of CPD, a plan for expected outcomes is useful. The least formal sources of CPD is the Internet, where an overwhelming amount of information related to issues in laboratory animal science is freely available. Without clear objectives or an assessment plan, it can be difficult for a veterinarian without formal training in the subject to know which information is relevant and valuable. Assessment of institutional veterinary competence will occur during periodic in-depth evaluations and reviews of the entire animal care and use program by external agencies such as AAALAC International or by institutional animal ethics committees (e. g. IACUC).

Part of the harmonization process of laboratory animal veterinary qualification depends also on the availability and accessibility of information. Several prestigious journals make articles freely available online several months after publication. PubMed, Georgetown library and the AAALAC International website can be excellent resources for information about laboratory animal medicine. The new Guide is also made available in 11 different languages, which is critical to advance knowledge of laboratory animal care and medicine in the world. It has also been proposed that a database of core references, including legal and scientific written in different languages could be created by the OIE.

Interpersonal skills play also a huge role for the laboratory veterinarians. The authors divide the types of interpersonal skills based on the kind of team of which the veterinarian will be part.

Animal Care team: The role of the veterinarian may be primarily clinical, with others responsible for gathering diagnostic evidence and delivering treatment. Excellent communication among team members is thus essential. Research Team: The role in this case may be to provide advice on clinical matters such as anesthesia, analgesia, and perioperative care, advice on relevant models for the research, including genetics and health status, and experimental design and planning. Negotiating skills in this case are going to be very important. Management team: in this case leadership and representation skill are important as well. Ethical review team: will require ability to advocate for moral and ethical issues, good communication, and effective negotiation and conflict resolution.

In the FELASA *Guidelines for the Veterinary Care of Laboratory Animals* (Voipio et al. 2008, 7), “In some countries, the ultimate responsibility for decisions concern- ing experimental procedures on, and euthanasia of, animals rests with the veterinarian, but in others it remains with the researcher. This may lead to conflicts....”. Such conflicts are best addressed when the veterinarian has credibility and good standing in the institution and has negotiated, before the start of the study, a framework for the decisions and actions to be taken to address animal health and welfare.

The principles of CPD are applicable to all veterinarians but are particularly relevant to practitioners of laboratory animal medicine because of rapid advances and changes in research.

The authors then concluded that consideration of training requirements in laboratory animal medicine and global harmonization of relevant veterinary qualifications is thus very timely and fully compatible with the OIE global mandate “to improve animal health, veterinary public health, and animal welfare worldwide.”

QUESTIONS:

1. What are at least 4 veterinary care program elements evaluated by AAALAC International during their program review?

2. What is the regulatory document for the oversight of animal use in research and teaching in the EU?

3. What does IACLAM stand for?

ANSWERS:

1. Animal procurement and transportation; quarantine, stabilization, and conditioning; surveillance, diagnosis, treatment, and control of disease; pain, analgesia, and anesthesia; surgery and postoperative care; and euthanasia.

2.  DIRECTIVE 2010/63/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 22 September 2010 on the protection of animals used for scientific purposes

3. International Association of Colleges of Laboratory Animal Medicine 