

## Policy on Drug Abuse Research with Laboratory Animals

Drug abuse research using laboratory animals has a long and productive history. Research with animals has enhanced our understanding of the biological, behavioral, and pharmacological causes and consequences of drug abuse, including drug intoxication, tolerance, reinforcement, dependence, and toxicity<sup>1-4</sup>. It has contributed significantly to the identification of specific brain regions and neurotransmitter systems that mediate the reinforcing effects of drugs that maintain drug use<sup>5, 6</sup>. Research with animals has also identified genetic, behavioral, and environmental factors associated with individual differences in vulnerability to drug taking<sup>7-9</sup>. Recent scientific advances have produced an explosion of knowledge about brain function and molecular biology, and research with animals will be required to apply this knowledge to problems of drug abuse.

From prevention to treatment, animal research has been critical in designing strategies that prevent drug abuse and developing treatment interventions to reduce drug abuse and prevent relapse during recovery. For instance, animal research has been instrumental in assessing the abuse liability of new prescription opioids and opioid formulations<sup>10, 11</sup>, thereby assuring that new drugs with significant risk of abuse are introduced with proper regulatory control and physician education. Animal research has also been critical in identifying the biological, genetic, and environmental factors that increase vulnerability to opioid addiction<sup>12-14</sup>. Furthermore, research with laboratory animals has been essential in the development of new medications for the treatment of opioid addiction, including novel formulations of buprenorphine and naltrexone<sup>15</sup>. It has contributed significantly to the development of opioid antagonists<sup>16</sup>, which have saved thousands of lives by quickly reversing the effects of unintended overdoses. Findings from animal models have also played a significant role in the development and refinement of behavioral methods for treating drug abuse and preventing relapse<sup>17-20</sup>. These same methodologies have been applied to the development of new drug abuse prevention and treatment strategies for other drugs, including cocaine, methamphetamine, nicotine, alcohol, and marijuana<sup>21-25</sup>.

The high morbidity and mortality associated with drug abuse underscores the need for research to develop better drug abuse prevention and treatment methods. From an economic perspective, the abuse of tobacco, alcohol, and illicit drugs is estimated to cost our nation more than \$740 billion each year in crime, lost work productivity, and health care<sup>26</sup>. These financial costs do not include the immeasurable personal suffering associated with drug abuse, or the extent to which drug abuse contributes to other social problems, such as HIV/AIDS, mental disorders, domestic abuse, unwanted pregnancy, and the rising incidence of newborns who experience neonatal abstinence syndrome because their mothers used drugs during pregnancy.

Research with drugs of abuse using laboratory animals helps us better understand a wide range of human disorders in addition to drug abuse. For example, the administration of drugs of abuse to laboratory animals has provided basic information concerning brain function, including mechanisms that underlie pain, memory, sleep, appetite, cognition, anxiety, depression, and social and emotional behavior<sup>27-35</sup>. This research, in turn, has contributed significantly to the development of numerous treatment medications, including new analgesics, anxiolytics, and antidepressants, as well as medications to treat a variety of other medical and psychiatric conditions<sup>36-40</sup>.

There is an urgent need to know more about novel drugs with significant abuse liability, particularly emerging drugs of abuse such as synthetic cannabinoids ("Spice", "K2"), synthetic cathinones ("Bath Salts"), and high-potency synthetic opiates (Carfentanil). The use of these

drugs has increased dramatically in recent years with parallel reports of severe toxicity and lethality<sup>41-43</sup>. Research with laboratory animals will play a key role in these efforts. Drug abuse is a pathology of behavior, and behavioral studies using live animals provide an essential complement to studies that examine underlying neurobiological mechanisms. Research with laboratory animals provides scientists with the means to study drug-related phenomena in the laboratory under controlled conditions using the best scientific methods available. Such research contributes significantly to our efforts to understand, prevent, and treat drug abuse and addiction. Careful attention to the well-being of the laboratory animals used in these studies is essential, not only for the safe and ethical conduct of the research but also for the quality and reliability of the research results.

Drug abuse research with laboratory animals in all countries must conform to all applicable national, state, and local laws and regulations that govern the use of laboratory animals in research. In the United States, such research must comply with federal regulations promulgated by the U.S. Department of Agriculture (USDA) under the Animal Welfare Act. If the research is federally funded, it must also comply with the U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals and the Institute of Laboratory Animal Resources Guide for the Care and Use of Laboratory Animals.

The College on Problems of Drug Dependence recognizes the value and importance of drug abuse research involving laboratory animals and supports the humane use of animals in research that has the potential to benefit human health and society. Such research plays a vital role in the acquisition of the new knowledge needed to understand and reduce drug abuse and its associated problems.

## References

1. Becker JB and Koob GF. Sex Differences in Animal Models: Focus on Addiction. *Pharmacol Rev.* 2016; 68: 242-63.
2. Nader MA. Animal models for addiction medicine: From vulnerable phenotypes to addicted individuals. *Prog Brain Res.* 2016; 224: 3-24.
3. Blanco-Gandia MC, Mateos-Garcia A, Garcia-Pardo MP, et al. Effect of drugs of abuse on social behaviour: a review of animal models. *Behavioural pharmacology.* 2015; 26: 541-70.
4. Lynch WJ, Nicholson KL, Dance ME, Morgan RW and Foley PL. Animal models of substance abuse and addiction: implications for science, animal welfare, and society. *Comp Med.* 2010; 60: 177-88.
5. Willuhn I, Wanat MJ, Clark JJ and Phillips PE. Dopamine signaling in the nucleus accumbens of animals self-administering drugs of abuse. *Curr Top Behav Neurosci.* 2010; 3: 29-71.
6. Koob GF. Neurocircuitry of alcohol addiction: synthesis from animal models. *Handb Clin Neurol.* 2014; 125: 33-54.
7. Belin D and Deroche-Gamonet V. Responses to novelty and vulnerability to cocaine addiction: contribution of a multi-symptomatic animal model. *Cold Spring Harb Perspect Med.* 2012; 2.
8. Winstanley CA, Olausson P, Taylor JR and Jentsch JD. Insight into the relationship between impulsivity and substance abuse from studies using animal models. *Alcohol Clin Exp Res.* 2010; 34: 1306-18.
9. Cadoni C. Fischer 344 and Lewis Rat Strains as a Model of Genetic Vulnerability to Drug Addiction. *Front Neurosci.* 2016; 10: 13.
10. Morgan MM and Christie MJ. Analysis of opioid efficacy, tolerance, addiction and dependence from cell culture to human. *Br J Pharmacol.* 2011; 164: 1322-34.

11. O'Connor EC, Chapman K, Butler P and Mead AN. The predictive validity of the rat self-administration model for abuse liability. *Neuroscience and biobehavioral reviews*. 2011; 35: 912-38.
12. Butelman ER, Yuferov V and Kreek MJ. kappa-opioid receptor/dynorphin system: genetic and pharmacotherapeutic implications for addiction. *Trends Neurosci*. 2012; 35: 587-96.
13. Eitan S, Emery MA, Bates MLS and Horrax C. Opioid addiction: Who are your real friends? *Neuroscience and biobehavioral reviews*. 2017; 83: 697-712.
14. Mague SD and Blendy JA. OPRM1 SNP (A118G): involvement in disease development, treatment response, and animal models. *Drug and alcohol dependence*. 2010; 108: 172-82.
15. Bailey CP and Husbands SM. Novel approaches for the treatment of psychostimulant and opioid abuse - focus on opioid receptor-based therapies. *Expert Opin Drug Discov*. 2014; 9: 1333-44.
16. Wallisch M, El Rody NM, Huang B, Koop DR, Baker JR, Jr. and Olsen GD. Naloxone pro-drug rescues morphine induced respiratory depression in Sprague-Dawley rats. *Respir Physiol Neurobiol*. 2012; 180: 52-60.
17. Banks ML and Negus SS. Insights from Preclinical Choice Models on Treating Drug Addiction. *Trends in pharmacological sciences*. 2017; 38: 181-94.
18. Bardo MT and Compton WM. Does physical activity protect against drug abuse vulnerability? *Drug and alcohol dependence*. 2015; 153: 3-13.
19. Lynch WJ, Peterson AB, Sanchez V, Abel J and Smith MA. Exercise as a novel treatment for drug addiction: a neurobiological and stage-dependent hypothesis. *Neuroscience and biobehavioral reviews*. 2013; 37: 1622-44.
20. Zhou Y, Zhao M, Zhou C and Li R. Sex differences in drug addiction and response to exercise intervention: From human to animal studies. *Front Neuroendocrinol*. 2016; 40: 24-41.
21. Banks ML. Utility of preclinical drug versus food choice procedures to evaluate candidate medications for methamphetamine use disorder. *Annals of the New York Academy of Sciences*. 2017; 1394: 92-105.
22. Bell RL, Hauser SR, Liang T, Sari Y, Maldonado-Devincci A and Rodd ZA. Rat animal models for screening medications to treat alcohol use disorders. *Neuropharmacology*. 2017; 122: 201-43.
23. Czoty PW, Stoops WW and Rush CR. Evaluation of the "Pipeline" for Development of Medications for Cocaine Use Disorder: A Review of Translational Preclinical, Human Laboratory, and Clinical Trial Research. *Pharmacological reviews*. 2016; 68: 533-62.
24. Panlilio LV, Justinova Z, Trigo JM and Le Foll B. Screening Medications for the Treatment of Cannabis Use Disorder. *Int Rev Neurobiol*. 2016; 126: 87-120.
25. Rahman S, Engleman EA and Bell RL. Nicotinic receptor modulation to treat alcohol and drug dependence. *Front Neurosci*. 2014; 8: 426.
26. <https://www.drugabuse.gov/related-topics/trends-statistics>.
27. Britton GB. Cognitive and emotional behavioural changes associated with methylphenidate treatment: a review of preclinical studies. *Int J Neuropsychopharmacol*. 2012; 15: 41-53.
28. Canales JJ. Comparative neuroscience of stimulant-induced memory dysfunction: role for neurogenesis in the adult hippocampus. *Behavioural pharmacology*. 2010; 21: 379-93.
29. Chagraoui A, Skiba M, Thuillez C and Thibaut F. To what extent is it possible to dissociate the anxiolytic and sedative/hypnotic properties of GABAA receptors modulators? *Prog Neuropsychopharmacol Biol Psychiatry*. 2016; 71: 189-202.
30. Gandelman JA, Newhouse P and Taylor WD. Nicotine and networks: Potential for enhancement of mood and cognition in late-life depression. *Neuroscience and biobehavioral reviews*. 2018; 84: 289-98.

31. Nogueiras R, Romero-Pico A, Vazquez MJ, Novelle MG, Lopez M and Dieguez C. The opioid system and food intake: homeostatic and hedonic mechanisms. *Obesity facts*. 2012; 5: 196-207.
32. Pasternak G and Pan YX. Mu opioid receptors in pain management. *Acta anaesthesiologica Taiwanica : official journal of the Taiwan Society of Anesthesiologists*. 2011; 49: 21-5.
33. Singewald N, Schmuckermair C, Whittle N, Holmes A and Ressler KJ. Pharmacology of cognitive enhancers for exposure-based therapy of fear, anxiety and trauma-related disorders. *Pharmacol Ther*. 2015; 149: 150-90.
34. Vanderschuren LJ, Achterberg EJ and Trezza V. The neurobiology of social play and its rewarding value in rats. *Neuroscience and biobehavioral reviews*. 2016; 70: 86-105.
35. Wang ZJ and Liu JF. The Molecular Basis of Insomnia: Implication for Therapeutic Approaches. *Drug development research*. 2016; 77: 427-36.
36. Xu Y, Barish PA, Pan J, Ogle WO and O'Donnell JM. Animal models of depression and neuroplasticity: assessing drug action in relation to behavior and neurogenesis. *Methods in molecular biology*. 2012; 829: 103-24.
37. Wilson C and Terry AV, Jr. Neurodevelopmental animal models of schizophrenia: role in novel drug discovery and development. *Clin Schizophr Relat Psychoses*. 2010; 4: 124-37.
38. Treit D, Engin E and McEown K. Animal models of anxiety and anxiolytic drug action. *Curr Top Behav Neurosci*. 2010; 2: 121-60.
39. Munro G, Jansen-Olesen I and Olesen J. Animal models of pain and migraine in drug discovery. *Drug Discov Today*. 2017; 22: 1103-11.
40. Yamada K and Nabeshima T. Animal models of Alzheimer's disease and evaluation of anti-dementia drugs. *Pharmacol Ther*. 2000; 88: 93-113.
41. Debruyne D and Le Boisselier R. Emerging drugs of abuse: current perspectives on synthetic cannabinoids. *Subst Abuse Rehabil*. 2015; 6: 113-29.
42. Paillet-Loilier M, Cesbron A, Le Boisselier R, Bourguin J and Debruyne D. Emerging drugs of abuse: current perspectives on substituted cathinones. *Subst Abuse Rehabil*. 2014; 5: 37-52.
43. Prekupec MP, Mansky PA and Baumann MH. Misuse of Novel Synthetic Opioids: A Deadly New Trend. *J Addict Med*. 2017; 11: 256-65.