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Editorial

Introduction and Summary to the Special Issue "Advances in the Neurobiological Basis of Inhalant Abuse"*

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This special issue of the Journal of Drug and Alcohol Research contains a series of papers originally presented at the 4th Meeting of the International Drug Abuse Research Society (IDARS) held in Mexico City April 15–19, 2013. Over 100 specialists from 15 different countries attended this conference, organized to promote research and collaboration of scientists around the world in the area of substances of abuse and addiction. The 2013 program covered relevant neuropharmacological, neurobehavioral, and neurochemical findings pertaining to the effects of commonly abused drugs in twelve plenary symposia and two poster sessions.

In this issue, we present findings from an IDARS symposium and related posters focused on abused inhalants, a common drug of abuse in many countries yet often understudied. The symposium, "Research on Inhalant Misuse: From Epidemiology to Epigenetics," was sponsored by the NIDA International Program and was organized and chaired by former NIDA INVEST fellow, Dr. Silvia L. Cruz (Cinvestav, IPN, Mexico) and NIDA funded researcher Dr. John J. Woodward (Medical University of South Carolina, USA). The presentations focused on the growing problem of inhalant abuse and sought to illuminate the progress that has been made in the study of these agents while highlighting key unanswered questions that remain. To encourage further collaboration and research into inhalant abuse, we present a series of five papers that encompass the work on inhalants presented at the 2013 IDARS meeting. A brief summary of each of these papers follows.

María Elena Medina-Mora, General Director of the Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz (Mexico), and coworkers review findings from epidemiology and psychosocial studies and discuss evidence that the use of inhalants (including solvents, fuels, gases, and nitrites) is a worldwide practice, with a higher incidence of use among children and adolescents in whom toxic effects are more detrimental than in adults. These studies indicate that inhalant misuse is increasing among young adults and that it is more common in poor communities with high violence and delinquency levels that often have significant populations of street children and adolescents. Although the voluntary misuse of inhalants is more frequent among males, the gender gap is narrowing as use among girls and young women increases. The risk of developing dependence to inhalants is well-established, with age at first use a significant predictor of future abuse. Among solvent users, suicidality and comorbidity with psychiatric disorders are also common and a family history of antisocial behavior is often observed. Regular users of inhalants are also more likely to show deviant behavior, school truancy, and lower academic performance. In general, abuse of inhalants increases the risk of morbidity and mortality and in particular, abuse of nitrites is associated with a higher risk of HIV. In spite of these findings that demonstrate significant health outcomes of inhalant users, the study of these substances has received less attention than other misused drugs. Dr. Medina-Mora et al. then discuss what is currently known regarding treatment of inhalant abuse that includes both pharmacotherapeutic and behavioral intervention approaches and the need for tailored-intervention programs. They conclude by suggesting that more studies including those involving epidemiology and psychosocial research are needed to draw attention to the gaps in our knowledge of inhalants and argues that neuroscience and clinical research efforts need to be combined with health policy options to reduce the harm associated with inhalant abuse.

*Preliminary versions of the papers featuring this special issue were originally presented at the 4th Meeting of the International Drug Abuse Research Society (IDARS) held in Mexico City, April 15–19, 2013.

Silvia L. Cruz (Cinvestav, Mexico) and colleagues present an overview of the current state of understanding of the molecular, cellular, and behavioral actions of toluene, the most widely abused inhalant. The authors emphasize that while it has long been known that individuals will engage in voluntary inhalation of volatile solvents for their rewarding effects, research into the neurobiology of these agents has lagged behind that of more commonly used drugs of abuse such as psychostimulants, alcohol, and nicotine. Dr. Cruz and coauthors review the literature and suggest that this paucity of knowledge has begun to shift in recent years as the deleterious effects of abused inhalants, especially among children and adolescents, on brain function and behavior have become better appreciated and scientifically documented. This review focuses on the physicochemical and pharmacological properties of toluene, a representative member of a large class of organic solvents commonly used as inhalants. It presents a brief summary of the clinical and preclinical evidence indicating that toluene and related solvents produce significant effects on brain structures and processes involved in reward. The authors highlight these findings with tables that summarize toluene's major effects on behaviors (reward, motor effects, learning, etc.) and cellular proteins (e.g., voltage and ligand-gated ion channels) closely associated with the actions of other commonly abused substances. As with Dr. Medina-Mora's chapter, these sections emphasize not only the progress that has been made in understanding the neurobiological basis for solvent abuse, but also reveal the many challenges that remain in developing a coherent understanding of the molecular and cellular targets of these often overlooked drugs of abuse.

John Woodward and Jacob Beckley (Medical University of South Carolina, USA) review the latest evidence on the neural effects of toluene on the mesolimbic dopamine system. As outlined in Dr. Cruz's chapter, research into the mechanisms of action of inhaled solvents has lagged behind that of other drugs of abuse despite evidence that these compounds exert profound neurobehavioral and neurotoxicological effects. Woodward and Beckley discuss how an interaction of solvents with a discrete set of ion channels may allow these agents to engage portions of an addiction neurocircuitry that includes midbrain and cortical structures. They focus on reviewing what is currently known regarding toluene's action on dopamine neurons in ventral tegmental area (VTA), a key midbrain region involved in the initial assessment of natural and drug-induced rewards. They describe experiments from their lab showing that brief exposures of adolescent rats to toluene vapor induce marked and long-lasting changes in markers of glutamatergic plasticity of VTA DA neurons. They show that these alterations are restricted to a subset of VTA DA neurons that project to limbic structures such as the nucleus accumbens while plasticity of DA neurons projecting to the cortex are unaffected. They then present data showing that the toluene-induced changes in mesolimbic VTA DA neurons are prevented by transient activation of the medial prefrontal cortex (mPFC) prior to vapor exposure. Conversely, pharmacologically blocking mPFC output allows a previous inactive dose of toluene to robustly increase glutamatergic plasticity of nucleus accumbens projecting VTA DA neurons. These findings are discussed in the context of a proposed neural circuit between the mPFC and the VTA that may explain these findings. Drs. Woodward and Beckley conclude their chapter by discussing the implications of these findings with regard to the treatment of inhalant abuse.

Keith Shelton and Katherine Nicholson (Virginia Commonwealth University, USA) present data from behavioral pharmacological experiments that allow comparisons of the abuse liability of different classes of inhalants. As pointed out by Drs. Shelton and Nicholson, inhalants are distinguished as a class only by their route of administration and as such represent a diverse group of chemical structures. While this classification has been useful, grouping inhalants according to their in vivo pharmacological effects has the potential to provide a more relevant classification scheme to the research and treatment community. With this background, the authors describe their work using the drug discrimination procedure to probe the sites of action of a group of inhalants. In these studies, mice learned to differentiate the interoceptive effects of trichloroethylene vapor from air using an operant behavioral procedure. Trichloroethylene is a chlorinated hydrocarbon solvent once used as an anesthetic as well as in glues and other consumer products. The results of these studies indicate that the stimulus effects of trichloroethylene are similar to those of other chlorinated hydrocarbon vapors, the aromatic hydrocarbon toluene, and the vapor anesthetics methoxyflurane and isoflurane. They also overlapped with those of the barbiturate methohexital, but less to the benzodiazepine midazolam or ethanol suggesting specificity of action. Compounds failing to substitute for trichloroethylene included NMDA receptor antagonists, the kappa opioid agonist U50,488, and the mixed 5-HT agonist mCPP. Drs. Shelton and Nicholson conclude their chapter by suggesting that the stimulus effects of chlorinated hydrocarbon vapors are mediated at least partially by positive modulatory effects on the $GABA_A$ receptor.

Carolina López-Rubalcava (Cinvestav, Mexico) and coauthors discuss data demonstrating the effects of prenatal binge toluene exposure on adolescent behavior. The continued abuse of inhaled organic solvents, especially among women of childbearing age, raises the risk of long-term behavioral effects of maternal toluene abuse. López-Rubalcava et al. discuss how prenatal exposure to

abused inhalants such as toluene in humans is associated with impairments in growth and development and is often accompanied by facial deformities often observed in cases of fetal alcohol exposure. They then review the small amount of preclinical data that have used animal models to study the effects of prenatal solvent exposure and review results from a recent study in their laboratory investigating the behavioral effects of prenatal and postnatal toluene exposure. In this study, independent groups of rats were treated at different times with toluene vapor and tested using a battery of behavioral tasks designed to assess levels of anxiety, pain perception, learning and memory, and motor activation. Results from these studies indicated that an acute exposure of postnatal rats to toluene produced anxiolytic-like effects in the burying behavior test. Rats exposed to toluene during both gestation (GD8–20) and adolescence (PN22–30) received the highest number of electrical shocks again indicating reduced levels of anxiety. Toluene exposure, either acutely or during both prenatal and postnatal periods, produced antinociception as measured by the hot-plate test while responses in animals exposed to toluene only in utero did not differ from controls. All toluene treatments also impaired short-term memory in the object recognition test, but only postnatal exposure produced significant impairments in long-term memory as measured by the passive avoidance test. Finally, while acute toluene induced locomotor activation, only animals exposed to toluene during both prenatal and postnatal periods showed sensitization to the locomotor enhancing effects of toluene. Overall, these results indicate that prenatal exposure to toluene can result in modification of selective behaviors in adolescent rats. Importantly, these effects occurred with a toluene concentration that did not produce evident craniofacial or physical malformations suggesting that the absence of physical alterations in humans prenatally exposed to toluene does not rule out more subtle alterations in behavioral and cognitive processes.

Together, the papers in this special issue emphasize how a translational approach that encompasses basic science and human studies is critical for fully understanding the nature of inhalant abuse worldwide. They also indicate the need for a more comprehensive and informative classification scheme for abused inhalants that better reflects differences in the pharmacological and behavioral actions of different types of inhalants. In addition, considerably more research is needed into developing possible treatment options for inhalant abusers since the current state of knowledge of this topic is modest and is often limited to small case studies. This is particularly compelling given that deficits in attention, learning, and behavioral control may persist long after solvent use is discontinued as evidenced by studies examining effects of prenatal and adolescent solvent exposure.

Finally, while it is clear that more work is needed to address the significant worldwide problem of inhalant abuse, the findings presented in this special issue also illustrate the tremendous advances that have been made in defining the targets and effects of the wide variety of agents inhaled for their rewarding and intoxicating effects. This understanding largely reflects the persistence of a small but growing group of basic and clinical scientists who have focused their time and attention on inhalant research and the willingness of national and international funding groups to support this important line of research.

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