Preface to the special issue of psychopharmacology: 10 years of the Jacob P. Waletzky Award

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The Jacob P. Waletzky award of the Society for Neuroscience was established in 2003 by the Waletzky family in memory of Jacob P. Waletzky who tragically died of cocaine-induced cardiac arrhythmia at the age of 29. In order to encourage research into the neurobiology of drug and alcohol addiction, the award, which carries a \$25,000 prize, is given each year to a young neuroscientist who has conducted innovative research in the area of substance abuse. At the tenth anniversary of the award, this special issue, edited by Klaus Miczek, Andrew Holmes, Marina Picciotto, and Yavin Shaham, presents a compilation of reviews and original articles by the first ten awardees: Pier Vincenzo Piazza (2003), Antonello Bonci (2004), William Carlezon (2005), Yavin Shaham (2006), Marina Picciotto (2007), Christopher Pierce (2008), Geoffrey Schoenbaum (2009), Paul Kenny (2010), David Jentsch (2011), and Andrew Holmes (2012).

The prestige of an award ultimately depends on the quality and impact of the work it recognizes, as also reflected in the stature of the awardees. On that account, the Jacob P. Waletzky award has become not only the premier award in addiction research but also one of the most coveted awards in the broad area of neuroscience for reasons that will be evident for the readers of this issue. The 11 papers in this issue (two by the Jentsch group)—a combination of reviews and original studies—provide the reader with a primer in the neurobiology of addiction and psychiatric disorders.

The review by Piazza and Deroche-Gamonet sets the stage by proposing a novel, three-phase theory for the natural history of drug addiction, according to which progression from recreational drug use to drug abuse occurs in vulnerable

individuals with an overactive dopaminergic system, and further progression to addiction occurs in those whose drug abuse leads to complete loss of synaptic plasticity. In the latter context, it would be very interesting to explore the role of the endocannabinoid/CB1 receptor system, which has a primary role in controlling synaptic plasticity, in the progression from abuse to addiction.

The group of Antonello Bonci presents a succinct review of the potential mechanisms of the pro-cognitive and potential therapeutic, anti-addiction, effects of modafinil, a long-acting, moderate affinity inhibitor of the dopamine transporter. The surprising efficacy of modafinil in reducing drug-taking behavior, possibly related to its ability to increase synaptic glutamate and its effects at mGlu2/3 receptors, is also discussed.

Van't Veer and Carlezon present a lucid review of the role of the dynorphin/kappa opioid receptor (KOR) system in close coordination with corticotrophin-releasing factor, as key mediators of the stress response, mediated both via the hypothalamic–pituitary–adrenal (HPA) axis and also through HPA axis-independent mechanisms in the brain. The ability of KOR antagonists to allay the negative consequences of chronic stress and thus improve stress resiliency is presented as a novel approach of not only treating, but may be preventing, psychiatric disorders, including drug addiction, precipitated by stress.

The Shaham group presents a timely review of the ever more complex mechanisms involved in drug reinstatement, as induced by drug re-exposure (priming), drug-related cues or contexts, or stress. The review highlights two recent developments: emerging evidence to indicate distinct differences in the brain structures and neural pathways involved in cocaine versus heroin reinstatement and the translational potential of results from rat studies using reinstatement models.

A hallmark of long-term nicotine exposure is the upregulation of high affinity ($\alpha 4\beta 2$) nicotinic acetylcholine receptors (nAChRs). These receptors and their regulation by

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nicotine are altered in psychiatric diseases, and this dysregulation may contribute to the high level of tobacco smoking and nicotine dependence in individuals with psychiatric illness. Lewis and Picciotto review the multiple molecular mechanisms involved in the upregulation of nAChR by nicotine in neurons and the abnormal expression and trafficking of nAChR in schizophrenia, bipolar disorder, and ADHD as deduced from postmortem and *in vivo* imaging studies. nAChR is also the topic of an original study by Kenny and colleagues, who used nAChR $\alpha 5$ subunit knockout mice to tease out the role of this subunit in the vulnerability to nicotine addiction via regulation of the aversive effects of high doses of nicotine. A polymorphism in this subunit is linked to both nicotine and alcohol dependence in human subjects.

Deep brain stimulation (DBS) has emerged as a promising therapeutic modality in a number of neurological and psychiatric conditions. More recent evidence suggests its potential therapeutic value in drug addiction, the topic of a review from the Pierce laboratory, which also examines the possible mechanisms underlying the beneficial effects of DBS in addictive states.

Geoffrey Schoenbaum and his group designed an experimental procedure in rats to demonstrate that cocaine self-administration disrupts neural circuits of model-based behavioral control, which allows one to recognize and use information about adverse outcomes. Understanding these circuits could help treat the cognitive disruptions that contribute to addiction. Loss of self-control over behaviors is also the topic of a paper by David Jentsch's group. In this paper, the authors

document changes in the striatal gray matter following chronic exposure of vervet monkeys to methamphetamine. These morphological changes correlated with altered inhibitory processes and were similar to changes detected in human methamphetamine users, thus indicating that they are the result of drug use rather than being a risk factor predating drug exposure. Another paper from the same group used mouse strains with different abilities for reversal learning, a measure of inhibitory control over impulsive responding, and found that poor reversal learning ability correlated with increased rates of cocaine self-administration and increased locomotor response to cocaine. Thus, a genetically determined deficit in behavioral inhibition may predispose to drug abuse.

Finally, Andrew Holmes with coauthors Rainer Spanagel and John Krystal reviews the emerging importance of the glutamate system in the pathophysiology of alcoholism. A particularly timely and forward-looking aspect of the review is a discussion of evidence suggesting that various glutamate receptors, receptor subunits, as well as glutamate transporters may be selectively targeted for the treatment of alcoholism.

An overarching theme in all of the papers in this special issue is a successful attempt to synthesize emerging new information about the complex neural circuitries and multiple neurotransmitter systems mediating substance abuse and related behaviors and identifying components of such circuitries as promising new therapeutic targets. A sense of justified optimism permeates these papers about the prospect of impending breakthroughs in the biology and treatment of substance abuse and addiction.