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The future is now: A 2020 view of alcoholism research

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The research presented in this Special Issue of *Neuropharmacology* emphasizes the profound evolution of alcoholism research during the past few years. Most notably, it demonstrates the substantial integration of basic science and human research across the three domains that are critical for the development of alcoholism, as shown in Fig. 1: Binge/intoxication, Withdrawal/negative affect and Preoccupation/anticipation. Superimposed on these domains are the neurobiological levels of analysis that range from molecular-genetic to synaptic-neurocircuitry.

At the molecular-genetic level, Reilly et al. (2017) sort genome-wide association studies of alcohol dependence and candidate human genes based on a functional framework across all addiction cycle domains. At the synaptic-neurocircuitry level, in the binge/intoxication stage, Harrison et al. (2017) focus on the brain regions and networks targeted by acute ethanol exposure in animal models, and the neurocircuitry of the basal ganglia is meticulously examined by Lovinger and Alvarez (2017).

In the withdrawal/negative affect domain, Pandey et al. (2017) describe the reprogramming of the epigenome in the amygdala and other brain areas associated with negative affect states in a model that integrates anxiety-like behavior with alcohol consumption. At the synaptic-neurocircuitry level in animal models, Roberto and Varodayan (2017) examine chronic alcohol-induced neuro-adaptations at GABAergic and glutamatergic synapses in different brain cells and regions, and the bed nucleus of the stria terminalis circuitry is explored by Vranjkovic et al. (2017). Relevant to both the withdrawal/negative affect and the preoccupation/anticipation stages, George and Hope (2017) review the amygdalar and cortical neuronal ensembles that are altered by alcohol in animal models. The stress-related neuronal to behavioral changes that are associated with chronic alcohol exposure and withdrawal in rodent models are presented by Becker (2017), including changes in pro-stress and anti-stress neuropeptide systems. Jimenez and Grant (2017) describe studies in macaque monkeys showing the relationship between alcohol and stress as risk factors and the consequences of daily drinking to intoxication, with an emphasis on the hypothalamic-pituitary-adrenal (HPA) axis. At the clinical level, Blaine and Sinha (2017) review the role of

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stress in the development of alcohol use disorder (AUD) as it relates to effects of alcohol on the HPA axis and glucocorticoid receptors in different circuits.

The preoccupation/anticipation stage necessarily engages human studies because elements such as “craving” remain challenging to measure in animal studies. At the molecular-genetic level, Warden and Mayfield (2017) discuss the transcriptional changes in the human alcoholic brain and the power of bioinformatics and sequencing techniques to present a systems-level view of the transcriptome throughout the addiction cycle. Also key to understanding the preoccupation/anticipation stage, considerable advances in brain imaging techniques have facilitated the study of addiction neurocircuitry in human subjects. Volkow et al. (2017) summarize the use of human brain imaging to study effects of acute and chronic alcohol consumption on brain metabolism and neurotransmitter function, and Zahr et al. (2017) highlight the neuroimaging studies in humans showing the prefrontal cortex-linked circuits affected by AUD.

The majority of the reviews include data from humans, often in the context of basic research findings in other species, including non-human primates, rodents, and even *Drosophila*. There is remarkable convergence of models and translation of results between species in alcoholism research today. One example of this convergence is in the evolving field of immune and neuroimmune signaling. Brain gene expression studies in humans and rodents show that excessive alcohol consumption perturbs immune-related genes in the brain as discussed in Warden and Mayfield (2017). *Drosophila melanogaster* has become an important model organism for alcohol research, and studies in *Drosophila* also link innate immune genes with alcohol sensitivity as reviewed by Park et al. (2017). These genetic and genomic alterations in immune/inflammatory pathways are translated to the protein and functional levels by Crews et al. (2017) who show that chronic alcohol exposure alters neuroimmune signaling in rodent and human brain, and that manipulations which counteract these signals can reduce alcohol consumption in rodent models. The role of immune dysregulation is carried to the clinical level by de Timary et al. (2017) who show that alcohol abuse alters immune function as well as the gut microbiome, suggesting that peripheral inflammation and intestinal dysbiosis are related to symptoms of AUD, such as depression, anxiety, and alcohol craving. These studies not only highlight the overlap in immune responses in laboratory models of alcohol consumption and human alcoholics but also the translational potential offered by this global approach. The neuroimmune system, as with other relevant systems-level responses, appears initially to affect all stages of addiction. As outlined in this Special Issue, discovery of neuroimmune and other alcohol targets based on cross-species genomic, cellular, and behavioral neuroadaptations systematically allows for identification of the conserved signaling pathways associated with AUD, providing a heuristic framework for advancing treatment strategies.

The clinical implications of research in the different domains of addiction are presented in the section on The future of diagnosis and pharmacotherapy. The article by Bell et al. (2017) on animal models for medication development showcases an extensive number of tables that provide one of the most complete compendiums of medication testing in rat models that has ever been assembled. Mason (2017) reviews the impressive progress in human laboratory studies of new pharmacotherapies, and Kwako et al. (2017) describe a potential evolution in

the clinical assessment of AUD. As highlighted in this Special Issue, the development of medications targeting the neurocircuitry and relevant gene networks (such as those involving brain reward/stress and immune systems) in different stages of addiction offers new possibilities to advance treatment for AUD.

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Fig. 1. Neurobiological-based framework for the stages of addiction.

A three-stage cycle of alcohol addiction, affecting synaptic-neurocircuitry and molecular-genetic systems, is shown. The brain regions are color coded to correspond to the relevant stage. ACC, anterior cingulate cortex; PFC, prefrontal cortex; DS, dorsal striatum; GP, globus pallidus; Thal, thalamus; NAc, nucleus accumbens; BNST, basal nucleus of the stria terminalis; CeA, central nucleus of the amygdala; HPC, hippocampus; OFC, orbitofrontal cortex; Insula, insular cortex. (The figure was modified from Volkow ND and Koob G, Brain disease model of addiction: why is it so controversial? *Lancet Psychiatry*, 2: 677–679, 2015).