

## Editorial

# Translational Research in Behavioural Pharmacology

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Increasing knowledge about disorders of the central nervous system in humans – better understanding the pathophysiology, developing more effective treatments, or both – is the long-term goal of a substantial portion of our animal studies. For that reason, the translatability of our experimental findings is of utmost importance. This translation, of course, can go both ways; either emulating the human situation in nonhuman subjects, or using results of animal studies to inform research in humans. In this Special Issue, we are deeply pleased to present 13 articles – 4 reviews and 9 empirical papers – that deal with this important matter.

The first article in this issue is a review by Cox and Reichel that addresses a topic that has received much attention in the last decade, empathy in animals. That is, do animals have empathic capacities comparable to humans? If so, how can these be experimentally investigated and how does this help us understand mental disorders characterized by social impairment in humans? This review introduces theories of empathy and provides an excellent summary of recent progress in studies on animal empathy, including underlying neural mechanisms and relevance for mental disorders. The second review, by Gipson and Bimonte-Nelson synthesizes two fields of interest that are rarely considered in combination, aging and addiction, with close attention to sex-related differences. Focusing on smoking and studies in women, this review discusses how age, hormonal influences, and tobacco use may affect normal and pathological aging and neurodegenerative diseases—identifying points of convergence and important areas for future research both in humans and animals. The third review, by Chaves Filho et al., addresses how neuroinflammatory processes may contribute to psychiatric disorders. In particular, the authors summarize preclinical and clinical studies investigating the efficacy of tetracyclines with neuroprotective and anti-inflammatory properties (such as doxycycline and minocycline) for the treatment of schizophrenia and mood disorders, thus providing a new perspective for treatment. The last of these four reviews, by Kandasamy and Morgan, proposes that home-cage wheel running be used as an assay for preclinical development of novel analgesic drugs. This idea is based on the mismatch between human and animal studies on pain, whereby restoration of function is a goal in the former, and inhibition of pain responses in the latter. The importance of restoration of function in the development of models to identify novel

analgesics has received increasing attention in recent years, and this represents an important step forward in preclinical research in this field. These reviews highlight the breadth of the topics addressed in this Special Issue, and of the field of translational behavioural pharmacology, ranging from social function to aging, addiction, mood disorders and pain, and including both fundamental questions and areas for innovative drug development.

Following up on these four reviews are a series of nine original research papers, again highlighting the diversity of research fields in which translational approaches in behavioural pharmacology are timely, including work on pain, anxiety, depression and addiction. The first of these, by Craft et al., investigates sex differences in the analgesic and anti-inflammatory properties of non-steroidal anti-inflammatory drugs. Importantly, these experiments demonstrate sex- and time-dependent effects of ibuprofen, ketoprofen and celecoxib on pain and inflammation. Next is an investigation by Fogaça Rosado et al., who show that the depression-like behaviour and cognitive impairments induced by chronic stress can be ameliorated by treatment with glibenclamide, a drug used for the treatment of type 2 diabetes. This drug has multiple targets and, in this study, appears to exert its effects by normalizing the stress-induced dysfunction of the hypothalamus-pituitary-adrenal axis. The following two papers also deal with mechanisms of mood disorders. Batista et al. introduce a model to study panic disorder in rats. They show that administration of the respiratory stimulant drug doxapram, in addition to producing its known effects on respiration, also decreased heart rate, increased blood pressure, evoked anxiety, and increased cellular activity in the periaqueductal gray. However, doxapram treatment did not result in conditioned place avoidance, suggesting an intriguing disconnect between these multiple measures associated with anxiety and/or stress and expected results in place conditioning. In a further comprehensive study, Lockington and Hughes investigated the effects of long-term treatment with the second-generation antipsychotic olanzapine on anxiety. Importantly, they assessed whether these effects depend on dose, sex and treatment length, using four different tests of anxiety. They found that long-term treatment with olanzapine was anxiolytic but, illustrating the complexity that can attend chronic treatment studies, that these effects were preceded by anxiogenic effects that were dose- and sex-dependent.

The final four articles in this Special Issue deal with addictive behaviour. The first, by Butler et al., includes complementary experimental work in humans and animals. This study demonstrates in both species that the reinforcing strength of nicotine predicts the vulnerability to cue-induced relapse, which not only provides important clues about mechanisms of relapse, but also lends credibility to the proposition that addiction-related behavioural paradigms in rodents have clear value for understanding addiction in humans. The next article, by Oinio et al. demonstrates that opioid neurotransmission differentially modulates cost-benefit decision making in a strain of rats bred for high levels of alcohol intake versus non-selected, outbred Wistar rats. Thus, this study provides a neural link between opioid-related vulnerability to alcohol addiction and a form of decision making that may be related to gambling behaviour. This article is followed by a fascinating study by Pallarés et al., who employ technology typically used to study brain function in humans, *in vivo* neuroimaging, to investigate alcohol drinking-induced neural activation in two strains of alcohol-preferring rats. They show divergent patterns of activation in cortico-limbic structures, with only limited overlap between the strains. These findings indicate that in individuals at risk for high alcohol consumption, the underlying neural and behavioural mechanisms may be very distinct, with important implications for translational studies on alcohol addiction, and for our understanding of the pathophysiology of this disorder in general. The penultimate article, by Laverde et al., shows that treatment with N-acetylcysteine, a drug that, among other actions, interferes with glutamate neurotransmission, blocked the development of alcohol-induced conditioned place preference in mice and also altered forebrain dopaminergic neurotransmission, thus revealing a potential mechanism for the blockade.

Importantly, the expression and reinstatement of place preference were not changed after N-acetylcysteine treatment. The issue closes with a report by Minnaard et al., who tested three candidate drugs for the treatment of human alcohol addiction in a model of alcohol drinking in rats. Their data show that treatment with baclofen and naltrexone, but not N-acetylcysteine, reduce voluntary alcohol intake in rats. Importantly, the effects of baclofen and naltrexone did not depend on baseline alcohol intake even though animals widely diverged in their levels of alcohol drinking, perhaps of relevance to differences in individual vulnerability to alcohol addiction in humans.

We think that these thirteen manuscripts represent important steps forward in translational research in behavioural pharmacology. Among other exciting developments, these papers present technologies used in humans that are applied in animals, investigate drugs used in humans in animal models, propose new models for analgesic drug development and panic disorder, link alcohol addiction to problem gambling and assess therapeutic versus potential side effects of a second-generation antipsychotic. In addition, we are pleased that there are two papers in this issue addressing sex differences in aging, addiction, pain and analgesia that very well illustrate the increasing awareness that investigation and comparison of animals from both sexes is imperative in moving our research fields forward. We thoroughly enjoyed editing these papers, and we hope that you will enjoy reading them.

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