Editorial

# Behavioural pharmacology and brain–body signalling processes

**Behavioural Pharmacology** 2018, **29**:99–101

Behavioural pharmacologists study the mechanisms by which drugs, and increasingly genomic and other manipulations, influence the ways in which organisms move through and interact with their external world. The fact that the brain is located within a body may pose unique challenges to scientific enquiry, as, for example, when care is taken to confirm that experimental results are not caused by sensory or motor impairments, or that they arise from a central rather than a peripheral site of drug action. But, there is a class of phenomena where, far from being irrelevant or inconvenient, interactions between the brain and the body are the main focus of the enquiry. Prime examples are pain and the so-called gut–brain axis. These phenomena are the subject of this Special Issue of Behavioural Pharmacology. As usual, this Special Issue contains a set of highly informative review papers followed by a longer set of papers reporting original and important research findings.

We open with two reviews – interestingly, from the same laboratory – introducing the two major themes. In the first, Roman and colleagues review the application of probiotics in the management of digestive, pain and emotional disorders. The authors survey the evidence from animal and human clinical studies that, by modifying the gut microbiome, probiotics – primarily lactic acid bacteria – have potential to treat gastrointestinal inflammatory conditions, functional gastric disorders, visceral pain, other pain disorders such as rheumatoid arthritis, and perhaps more surprisingly, anxiety and depression. (The text is supplemented by helpful summary tables.) They consider in detail the physiological mechanisms that are thought to underlie these effects, and call for larger and more definitive clinical trials. The second paper, by Lopez-Perez and colleagues, considers the role of neurotropins in pain production and sensitization. The role of nerve growth factor and brain-derived neurotropic factor in somatic pain has been extensively studied and is reviewed here; but the major focus is on the less fashionable area of visceral pain, particularly functional disorders (those that arise with no obvious structural pathology) such as inflammatory bowel disease and irritable bowel syndrome. Mechanisms for pain sensitization include neurite outgrowth, and activation of TRPV1 channels and other molecules relevant to nociception, and may involve epigenetic programming by early life stress. The authors note that antibodies against nerve growth factor and brain-derived neurotropic factor have had some success in preclinical models of visceral pain, but that this strategy has not yet been tested in humans.

The Special Issue continues with two authoritative reviews of heart-rate variability (HRV). Both reviews begin with a comprehensive and informative exposition of the many indices that are used to measure HRV. The first review, by Young and Benton, considers the extent to which HRV can serve as a biomarker to study the influence of diet on physiological and psychological health. The authors note that, as the influence of diet on health may take place over a period of decades, there is a need for biomarkers that help to identify those aspects of nutrition that have either a positive or negative influence. They review the evidence that those diets (e.g. omega-3 fatty acids) that are considered healthy reliably increase HRV, whereas those that are considered unhealthy (e.g. trans-fats) decrease HRV, and argue that HRV can be considered as an index of psychological and physiological resilience, which can serve as an indicator to identify potentially beneficial or detrimental aspects of diet. In the second review, Kidwell and Ellenbroek consider the relationship between HRV and major depression. There is a bi-directional relationship between major depression and cardiovascular disease, each increasing the risk for the other, and HRV has often been suggested as a potential mediator of this co-morbidity. The authors review how HRV is altered in major depression (greater variability is healthier) and how HRV is affected by antidepressant drugs (which have both negative and positive effects) and other treatments, with a particular focus on vagal nerve stimulation, as well as the mechanisms underlying these effects.

In the final review paper, Barreto and colleagues consider the link between depression and cancer. Both are characterized by a dysregulation of inflammatory and immune pathways. The authors argue that an important mediator is the enzyme indoleamine 2,3-dioxygenase (IDO), the rate-limiting enzyme of the tryptophan catabolite pathway. IDO is induced by inflammatory markers and oxidative stress, and the resulting tryptophan catabolite metabolites suppress various markers of immune function. While emphasizing that both depression and cancer


DOI: 10.1097/FBP.0000000000000401

are heterogeneous conditions, the authors consider whether IDO might serve as a pharmacological target for the treatment of co-morbid and cancer depression.

The gut–brain axis is the target of the first three empirical studies reported, which explore the effects on the gut of manipulations that are considered as animal models of psychiatric disorders. The first paper describes a study by Morais and colleagues of the effects on the gut of maternal immune activation (MIA) with with polyinosinic–polycytidylic acid. This treatment causes deficits of social behaviour in the offspring that provide an animal model of aspects of autism. Here, MIA was applied to two mouse strains that differed in their sensitivity to MIA-induced social deficits. It was found that MIA also caused parallel changes in gut permeability. These data may shed light on the observation of gastrointestinal abnormalities in autism that have sometimes been mistakenly considered as causative. In the second paper, Morais and colleagues note that environmental factors, such as exposure to pesticides, may play a role in the onset of some forms of Parkinson's disease and that early signs of Parkinson's disease can appear in the gastrointestinal tract and in the olfactory system long before the onset of motor impairments. The pesticide rotenone is known to cause degeneration of dopamine (DA) neurons and Parkinsonian symptoms. Here, it was shown that 7 days of treatment with rotenone caused leucocyte infiltration in the colon, associated with histological damage and disrupted gastrointestinal motility, and also disrupted olfactory discrimination in mice, in the absence of locomotor deficits. The third study, by Jung and colleagues modelled another DA-dependent psychopathology, obsessive–compulsive disorder, using chronic administration to rats of the DA D2/D3 agonist quinpirole. The development of compulsive checking behaviour and locomotor sensitization was accompanied by changes in several communities of gut bacteria. The authors suggest that these changes may serve to support the energy utilization requirements of compulsive checking and OCD.

With a continued focus on DA, the next two studies evaluated the role of dopaminergic mechanisms in periaqueductal gray (PAG)-mediated antinociception. Tobaldini and colleagues used intra-PAG injections in rats to study the involvement of DA receptors in on mu-opioid-mediated thermal antinociception. Using DA receptor agonists and antagonists they found evidence for involvement of both D1-like and D2-like receptors, with a more pronounced role for D2-like receptors, which was GABA dependent. Moreover, using intra-PAG injections, Schoo and colleagues found that the antinociceptive effect of the nonselective DA agonist apomorphine was enhanced by systemic administration of the mu-opioid receptor antagonist naloxone. This implies that dopaminergic agonists and mu-opioids differ in their mechanism of antinociceptive action, which, the authors suggest, could provide a novel approach to pain relief.

The next two papers also consider aspects of mu-opioid antinociception. Grenier and colleagues addressed the problem that the value of opioid analgesics is limited by tolerance development (as well as undesirable side effects), asking whether antinociceptive tolerance would be attenuated by concomitant treatment with an ultra-low dose (ULD) G-protein-coupled receptor antagonist. Opioid tolerance of rats in a thermal tail-flick test was indeed attenuated by ULD $\alpha_2$-adrenergic antagonists, though not by ULD treatment with a cannabinoid CB1 receptor antagonist. The authors refer to some clinical support for the ULD concept in pain control. In the third study in this series, Pachenari and colleagues report on the apparent transgenerational transmission of pain perception. They found that paternal morphine exposure did not affect their offspring's sensitivity to morphine in the formalin test, but morphine-sired and saline-sired rats did differ in a small detail of the time course. These may be of limited clinical significance, but transgenerational effects, particularly those from the father, are of increasing interest.

The next three studies reported in this Special Issue evaluated potential novel antinociceptive agents. Nasu and colleagues studied the effect of neurotropin, an extract of rabbit skin inflamed by inoculation with vaccinia virus, which is used in China and Japan for treatment of chronic pain. Intramuscular administration of neurotropin was without effect in control rats, but reduced mechanical hyperalgesia induced by repeated cold stress. This effect was seen bilaterally, and blocked by GABAergic, serotonergic, cholinergic and mu-opioid receptor antagonists. Quiñonez-Bastidas and colleagues studied the effect of (−)-epicatechin in models of inflammatory pain, following reports of antinociceptive effects of catechins. They found that (−)-epicatechin reduced nociception induced by carrageenan, formalin and nerve injury. The effects were blocked by antagonists at multiple 5-hydroxytryptamine and opioid receptors as well as agents acting at multiple points in the NO-cyclic GMP-$K^+$ channels pathway. Craft and colleagues compared the effects in male and female rats of the cannabinoid CB2 antagonist JWH015, in acute (paw withdrawal) and chronic inflammatory (complete Freund's adjuvant) pain models, noting that the antinociceptive effects of CB2 antagonists have rarely been studied in females. JWH015 had antinociceptive effects in both models, with broadly similar effects in males and females.

The final paper in this Special Issue reports a methodological study by Legakis and colleagues of the cancer chemotherapy paclitaxel. Paclitaxel has adverse effects, including peripheral neuropathy and neuropathic pain, which in rodents are observable as hypersensitive paw

withdrawal reflexes from mechanical stimuli. This study investigated whether adverse effects of paclitaxel would also be observable as depressed rates of positively reinforced operant behaviour. However, at doses causing mechanical hypersensitivity in rats, paclitaxel did not reliably depress rates of intracranial self-stimulation, perhaps questioning the value of this pain-depressed behaviour assay.

The range of reviews and empirical reports in this Special Issue makes it abundantly clear that the study of brain–body signalling processes is a fertile area of behavioural pharmacology. The examination of internal sensory processes and their impact on ongoing behaviour and, in turn, biological substrates, is not a new science; the role of brain–body interactions in the effects of drugs has been long recognized. However, the difficulties in conducting objective experimentation on the role of internal processes in brain function have tended to dampen this type of research. It is not an easy work, and a great care must be taken to enunciate the experimental question concretely, to insure rigour in the methodology and to interpet results cautiously. Nor are the relationships that can be defined are necessarily linear; that is, as body processes influence brain function and vice versa, it can be particularly difficult to tease apart causal and co-variate factors. Yet, this is an incredibly important area of behavioural pharmacology to continue to develop. The contributions in this Special Issue show both that impressive inroads already have been made and, not surprisingly, there is much left for us to do.

As featuring pain research in a Special Issue some years ago, Behavioural Pharmacology now receives a healthy flow of manuscript submissions reporting studies of mechanisms of and treatments for acute and chronic pain. The other areas addressed in this Special Issue, the gut–brain axis and heart-rate variation are new departures. We would welcome further empirical submissions in these important areas.

Paul Willner (Editor)
Jack Bergman (Associate Editor)
Louk Vanderschuren (Associate Editor)
Bart Ellenbroek (Reviews Editor)