Editorial

The behavioural pharmacology of stress-related disorders

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Our aim when planning this Special Issue was to showcase behavioural pharmacology research relevant to stress-related disorders, with a focus on lasting consequences of stress and a particular interest in post-traumatic stress disorder (PTSD). We are pleased to present an impressive collection of papers that opens with seven reviews, fully five of which deal with aspects of PTSD.

The first paper provides a comprehensive review of animal models of PTSD. Such models are difficult to establish because of the limited understanding of the heterogeneity of PTSD, the variable presentation (depending to some extent on whether the condition arises from a single traumatic event such as a road traffic accident or from more extensive trauma such as a history of abuse), and the limited efficacy of currently available pharmacotherapies. This review, by Aspesi and Pinna, describes the behavioural and neurobiological features of the animal models of PTSD that are in current use, pointing out that most of them can reproduce not only behavioral endophenotypes, including anxiety-like behaviors or fear-related avoidance, but also neurobiological alterations, such as glucocorticoid receptor hypersensitivity or amygdala hyperactivity, that are characteristic of PTSD. The authors focus in particular on a mouse social isolation model studied in their laboratory, and point to neurosteroid biosynthesis and the interaction of neurosteroids with the endocannabinoid system as promising avenues for novel pharmacotherapies.

One of the preeminent symptoms of PTSD is avoidance of trauma-related stimuli. The second review, by Albrecht-Souza and colleagues, focuses on a particular animal model, avoidance of predator odour by rats, which (consistent with PTSD symptomatology in humans), varies in intensity among individuals. The paper describes the behavioural (e.g. compulsive-like alcohol self-administration) and neurobiological (e.g. higher corticotropin-releasing factor levels in multiple brain regions) features of high-avoider rats following exposure to a traumatic stressor. The authors emphasize the etiological validity of their model, and the utility of incorporating an individual differences approach.

The third review, by Cabib and colleagues, advocates a dimensional approach to the development of animal models of PTSD, based on candidate endophenotypes that could include genetic liability factors, variations in symptoms profile and underlying neurobiological mechanisms, and specific comorbidities. They focus on two specific endophenotypes, low sensory gating and high waiting impulsivity, and review the evidence that these are both present in the DBA/2J mouse strain, but absent in the genetically unrelated C57BL/6J strain. The DBA/2J mice also show stress-induced extinction-resistant avoidance, as expected in a model of PTSD, but also neural and behavioral phenotypes promoted by prolonged exposure to addictive drugs, suggesting a role of genotype in determining different PTSD comorbidities.

In the fourth review, Murnane considers the role in PTSD of the 5-HT_{2A} receptor, which is the major excitatory serotonin receptor in the brain and which has been linked to the effects of drugs that produce profound sensory and cognitive changes. It is proposed that stress, particularly stress related to danger and existential threats, increases the expression and function of 5-HT_{2A} receptors as a neurobiological adaptation to promote learning and avoidance of danger in the future. The argument is that upregulation of 5-HT_{2A} receptors during stressful events forms associations that tune the brain to environmental cues that signal danger which, when triggered, contribute to the symptoms of PTSD. Somewhat paradoxically, 3,4-Methylenedioxymethamphetamine (MDMA), which also indirectly activates $^{5\text{-HT}}$2A receptors, has recently been recognized as a potential therapy. This will clearly be an exciting area to watch as the story unfolds.

The final PTSD review, by Hoffman and Taylor, focuses on traumatic brain injury (TBI), which significantly increases the risk for comorbid PTSD. The authors summarize evidence that TBI causes HPA axis dysregulation, as well as enhanced fear and increased amygdalar function, and they present the hypothesis that TBI increases vulnerability to development of PTSD following traumatic stress by impacting on the amygdala and brain defense mechanisms to increase stress reactivity.

The final two review papers in this Special Issue, rather than focusing on PTSD, deal with the neurobiology of stress more generally. The first, by Barone, presents a comprehensive overview of tryptophan metabolism an important but perhaps under-recognized topic. Behavioural pharmacologists tend to overlook the fact that only around 5% of tryptophan is metabolized to serotonin, a central preoccupation of behavioural pharmacology, while the other 95% is metabolized to kynurenin. Depending on the balance of activity among several enzymes, kynurenin is further metabolized either to excitotoxic end-products such

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as quinolinic acid, or to kynurenic acid, which is neuroprotective. Importantly, most of these metabolites cross the blood-brain barrier, leading to profound consequences within the brain. It is argued that during stress, the production of cytokines and other inflammatory modulators shifts the balance towards the excitotoxic branch of the tryptophan catabolites pathway, leading to neurodegeneration, which is now known to be an important factor underlying depression and other psychiatric disorders. It is further proposed that shifting the metabolic balance back towards the neuroprotective branch could be an important strategic target for more effective treatment of mood disorders. Looking forward to the next Behavioural Pharmacology Special Issue (towards the end of this year), which will be on Neuroinflammation, we hope to see more on this topic.

And looking back to this time last year (the Special Issue on Behavioural pharmacology and brain–body signalling processes, Behavioural Pharmacology 29.2-3), the final review paper in this Special Issue addresses stress and the gut-brain axis. Molina-Torres and colleagues review both the effects of stress on the gut microbiota and how modulation of the gut microbiota may influence the stress response. They conclude that there is clear preclinical evidence of effects in both directions. Furthermore, although the clinical evidence is more limited, there are sufficient data to argue that a better understanding of the mechanisms underlying stress modulation through the microbiota could open new avenues for the treatment of common mental disorders such as anxiety and depression.

The Special Issue continues with nine reports of original research, the first three of which are relevant to PTSD and the remainder to other stress-related disorders. The first, by Alzoubi and colleagues, utilized a widely used animal model of PTSD, single prolonged stress (SPS) in rats. SPS is known to impair memory (here measured using a radial arm water maze) and to increase measures of oxidative stress. The study demonstrates that both of these effects were prevented by chronic administration of a neuroprotective agent, edavarone. The two following studies, both by Kosari-Nasab and colleagues, studied anxiogenic effects (using multiple tests in mice) of mild TBI, which as noted above, predisposes to PTSD. Both the anxiogenic effects and HPA hyperactivity following TBI were prevented by chronic post-treatment with the CRF antagonist antalarmin, and the antioxidant flavonoid quercetin, suggesting therapeutic potential of both compounds in TBI and perhaps PTSD.

In the next paper, Willner and colleagues present a validation of chronic mild stress (CMS) in the Wistar-Kyoto (WKY) rat as a model of treatment-resistant depression (TRD). It has been proposed that an animal model of TRD should meet four criteria: a phenotypic resemblance to a risk factor for depression; enhanced response to stress; non-response to antidepressant drugs; and responsiveness to treatments effective in TRD, such as deep brain stimulation (DBS) of the prefrontal cortex (PFC) or ketamine. This paper demonstrates that the WKY rat subjected to CMS meets all four criteria. In particular, although the commonly reported anhedonic, anxiogenic and dyscognitive effects of CMS were all reversed by chronic treatment with different antidepressant drugs in Wistar rats, WKY rats were non-responsive to antidepressant treatment. However, in WKY rats, while standard antidepressant drugs were ineffective, all of the effects were reversed by DBS of the PFC and by ketamine. This brings into play an important new preclinical tool for the discovery and development of treatments for the high proportion of patients who are antidepressant non-responders.

A further paper treats CMS as an animal model of obsessive-compulsive disorder (OCD), on the basis that in addition to the anxiogenic effect of CMS, there is also a compulsive effect that can be revealed by the marble-burying test. Garabadu and Kumar show in this study that celecoxib, a drug that is used adjunctively alongside fluoxetine in the treatment of OCD, reversed the anxiogenic and pro-compulsive effects of CMS, as well as associated increases in levels of serotonin in the prefrontal cortex and a raft of pro-inflammatory markers. Celecoxib also potentiated the effects of fluoxetine, as observed clinically. The authors speculate that a combination of celecoxib and fluoxetine may be a better option for the treatment of OCD, particularly in patients for whom fluoxetine alone is ineffective.

The third paper in this group, by Dixon and colleagues, concerns long-term effects of early life stress (ELS), which increases the risk for a range of mental health problems, including addictions. The study was based on the evidence that a polymorphism of the *GABRA2* gene, which encodes the α2 subunits of $GABA_A$ receptors, increases risk for both PTSD and cocaine addiction. The authors applied a model in which the amount of material for nest building was reduced during early postnatal life to knockout mice lacking α2 subunit-containing $GABA_A$ receptors. They report a complex set of data on locomotor stimulation by cocaine, behavioural sensitisation to repeated cocaine, and cocaine-conditioned activity. They conclude that the ability of ELS to increase cocaine-conditioned locomotor activity appears to be independent of α2-containing $GABA_A$ receptors.

Moving to a rather different context, catalepsy induced by haloperidol – an immobile state in which subjects fail to change imposed postures is very similar to that observed in Parkinson's disease (PD). Based on the observation that some PD symptoms depend on the patient's emotional state, and anxiety disorders are common in PD, Barroca and colleagues examined the modulation of haloperidol-induced catalepsy by a variety of different acute stressors. Most of the stressors examined (e.g. foot-shock) had no significant effect on haloperidol-induced catalepsy, but contextual conditioned fear, which is thought to be more intense, increased catalepsy over time. This suggests that it may be worthwhile

to examine whether the specific environmental stressors that engage defensive circuits may be particularly adverse for PD patients.

In the penultimate paper in this series, Grahn and colleagues aimed to understand the common observation that behaviour on the elevated plus maze, a mildly stressful experience that is widely used to measure anxiety-like behaviour in rodents, is different on a second exposure: specifically, the behaviour on a second trial is less responsive to anxiolytic drugs. The authors were able to relate the different responses to the benzodiazepine chrolordiazepoxide on first and second maze exposures to activity in specific patterns of 5-HT neurons in the dorsal raphe nucleus. And, finally, van den Bos and colleagues have studied the effects of exposure to cortisol, mimicking ELS, on the behaviour and physiology of two strains of juvenile zebrafish. The data suggest that ELS has robust effects on the development of zebrafish larvae, which are strain dependent, and provide encouragement that zebrafish, with the advantage of rapid growth and development, could provide an alternative model to study the effects of ELS on life history.

Altogether, we are excited to see the publication of this series of reviews and original research articles on stress-related disorders. The breadth of topics addressed in this Special Issue highlights how lively this area of study continues to be, and we are pleased that the diversity of approaches and lines of thought in this important research field are reflected here.

Paul Willner
Jack Bergman
Louk Vanderschuren
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