Neuropharmacology 159 (2019) 107784

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Editorial

The neuropharmacology of social behavior: From bench to bedside

This Special Issue of Neuropharmacology on the topic of social behavior was organized with invitations for reviews and original articles. Contributors were invited to cover what makes social behavior such a cross-cutting transversal/quasi-ubiquitous aspect of modern neurosciences. Beside its obvious – and genuinely fascinating-anthropomorphic value, social behavior in rodents is an incomparable tool to identify the brain areas and synaptic circuits as well as the cellular and molecular pathways underlying major behavioral deficits associated with neurodevelopmental (e.g. schizophrenia, autism), neuropsychiatric disorders (e.g. addiction, depression) and traumatic brain injury.

The success and pervasive interest of social behavior in "brain" research is evidenced by the number of PubMed hits for "social behavior and brain" since 1946 to this day (Fig. 1). Most striking is the sharp rise in publications in the new millennium. After all isn't the modern world that of social media?

This Special Issue of Neuropharmacology starts with a review by Ghosal et al. (2019) who define the neuropharmacology of the circuits underlying social hierarchies. Indeed, social groups across species organize into hierarchies based on individual differences in social dominance. As shown in this review, the benefits of a high social status points to a key role of the mesolimbic system (and associated circuits) and in the neurochemical fabric of dominance. Dominant rodents do not care for their social media status, but their mesolimbic circuits rely on dopamine signaling, GABAergic neurotransmission, the androgen receptor system and bioenergetics to reap the rewards (food, territory, mating partners) associated with the hierarchical position.

Next, Pelloux et al. (2019) address the fascinating links between social interactions and drug use/addiction. They first carefully review how distal social factors (i.e. hierarchical status, past social experiences and early life events) influence drug use and then move on to describe new and exciting results showing how social interaction during drug-taking, the so called-proximal factors, shapes drug use and addiction.

In rodents, the major mean of proximal social communication is ultrasonic vocalizations (USV). The review by Simola and Granon (2019) provides an overview of the behavioral significance of USV communications and importantly describes how to best use USVs as a marker of effects in rat and mouse models of emotional disturbances (e.g. stress, anxiety, depression), psychosis, developmental diseased (e.g. autism spectrum disorder ASD, schizophrenia), drug addiction and neurological disease (e.g. Parkinson disease, trauma).

ASD has become one the most visible and widely studied disease of social behavior. Tartaglione et al. (2019) provide an update of preclinical studies on prenatal exposure to valproic acid (VPA) a widely prescribed epilepsy drug that increases risk of autism in human and rodent offspring. While the data so far support the VPA model as a reliable tool to investigate the underpinnings of ASD-linked social impairment and thus identify new drugs to cure the disease, the authors also highlight potential pitfalls and future directions in this exciting research field.

In the last review of this Special Issue, Keum and Shin (2019) present what is undoubtedly one of the next frontiers of social neuroscience: empathy. In humans and rodents, emotional experience and social interactions require neurocognitive ability to recognize and share the mental states of others. The review first summarizes aspects of empathy at the behavioral and circuit levels and highlights new rodent behavioral paradigms. In contrast with classical social behaviors that intensely engage the mesocorticolimbic system, empathy circuits include the anterior cingulate and insular cortices. The authors next show that the neurochemical underpinnings of empathic abilities are remarkably similar to those highlighted in the previous reviews: oxytocin, dopamine, serotonin, opioid receptors and testosterone. Finally, the genetic polymorphisms associated with individual differences in empathy are discussed.

This Special Issue ends with five original Research Papers. Godar et al. (2019) characterize a new model of gene-environment (GxE) interactions that models antisocial behavior. They studied the neurobehavioral phenotypes of monoamine oxidase A hypomorphic transgenic mice expose to early life stress. Mice exposed to stress specifically between postnatal day 1 and 7, had upregulated prefrontal $5HT_{2A}$ receptors and developed antisocial behavior from the fourth week onwards. Strikingly, the authors then show that inhibition of $5HT_{2A}$ receptors normalizes the neurobehavioral deficits.

Frau et al. (2019) used the same GxE model but focused on pre-adolescence by performing extensive behavioral analyses in parallel to electrophysiological appraisal of ventral tegmental dopamine and prefrontal neurons. The results show how pre-adolescent aggressive behavior is accompanied with altered excitability and aberrant synaptic plasticity. Finally, blocking D1 receptors rescued both aggressive behaviors and PFC function. Together these two papers highlight the role of monoamines systems in the ontogeny of GxE linked antisocial behaviors.

The paper by Achterberg et al. (2019) focuses on the role of opioid neurotransmission in the pleasurable and motivational properties of social play behavior in rats. Social play is the most characteristic social behavior displayed by mammals between weaning and sexual maturation; it is both highly rewarding and crucial for proper neurobehavioral development. The authors used an operant conditioning setup in which rats responded for social play under a progressive ratio schedule of reinforcement, and a social play-induced conditioned place preference procedure. The data reveal that opioid neurotransmission is involved in both the pleasurable and the motivational aspects of social play behavior.

In their Research Paper, Faure et al. (2019) illustrates some of the concepts developed in the reviews by Simola and Granon (2019) and

https://doi.org/10.1016/j.neuropharm.2019.107784

Available online 18 September 2019

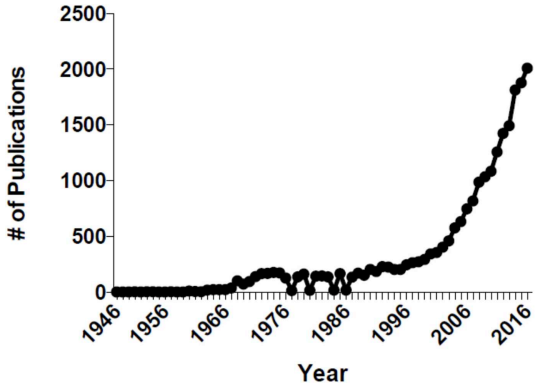

Fig. 1. PubMed citations from 1946 to 2019 using the search term "social behavior and brain".

Pelloux et al. (2019) in this Special Issue. In three mouse models for schizophrenia with social dysfunction they evaluated vocal communication defects. In their schizophrenia models, they show that USV emissions are reduced during social interaction. This study suggests that their current social interaction protocol, combined with principal component analysis of interaction and communication data, may provide an innovative framework in the evaluation of preclinical models.

The last paper, by Miao et al. (2019), provides experimental evidence to the critical role of psychological support and bond in social buffering. Social avoidance and anxiety-related behaviors induced in male mice by chronic social defeat stress were alleviated by the presence of their pregnant partner without active body contact during the stress process, whereas nonpregnant females did not afford a similar protective effect to the male partner. Interestingly, the psychological buffering induced by the presence of the pregnant partner were inversely correlated with BDNF levels in the hippocampus.

Collectively, the reviews and research articles included in this special issue illustrate the two principal currents that in our view, will guide social behavior studies in the forthcoming years: 1. decipher the circuits/neuronal architecture underlying social behavior in health and disease states; 2. the quest for translational anthropomorphic models to dissect the different facets of the social brain.

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