Brain serotonin throughout development-for better and for worse

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Valorisation

Psychopathological manifestations, such as fear and anxiety disorders in the form of posttraumatic stress disorder (PTSD) and generalised anxiety disorder (GAD), or aggression and impulsivity are a major social burden in today’s society (Penden, McGee and Krug, 2000; World Health Organization, 2001, 2002; Kessler and Greenberg, 2012; American Psychiatric Association, 2013; Chisholm et al., 2016). Symptoms, including excessive worry, avoidant behaviour or panic attacks as well as inflicting harm on others or self, impair patients in everyday life and are putting a strain on communities and families. Next to the social component, the economic burden, imposed by the treatment of symptoms and dealing with direct and indirect consequences of the disorders, is substantial. According to the global burden of disease estimates, undertaken in the 1990ies, mental disorders are amongst the most costly disorders, causing up to 10.5% of all disability-adjusted life years (DALYs) lost (Murray and Lopez, 1996). A foremost reason for this unproportional representation of mental disorders in the global burden of disease estimates, might be found in the historic stigma, accompanying mental disorder and concomitant behavioural aberrations. In consequence, insufficient means and treatment have been provided giving way to secondary consequences, such as long-term disability, resulting in unemployment, or anxiety-related underemployment (World Health Organization, 2001; Kessler and Greenberg, 2012) and, in the case of pathological aggression, in injury and e.g. sexually transmitted diseases (World Health Organization, 2002). For both patients and society, it is relevant to extend the current understanding of the underlying brain circuitries and molecular mechanisms of overshooting fear and anxiety, antisocial behaviour and other related traits, in order to promote more efficient, targeted, and individual treatment options.

Only in recent years, mental disorders have been accepted as vital contributor to an individual’s health and well-being. Simultaneously, the field of neuroscience has experienced a boost, making use of advances in imaging techniques and in the field of genetics and molecular biology. In particular, one line of research proved promising in closing in on the roots of mental disorders, by focussing on a joint approach of gene-environment-based psychiatric research and neuroscience (Caspi and Moffitt, 2006). A prominent factor that has emerged from all related investigations and was identified as one of the first proofs of this combined approach is the serotonin (5-hydroxytryptamine, 5-HT) system. The 5-HT system comprises multiple levels of effect and exerts a multitude of functions throughout development (Gaspar, Cases and Maroteaux, 2003). It is known as neuromodulator and regulates the excitability of neurons (Andrade, 1998). Furthermore, genetic variants that were identified in genes, encoding relevant factors of the 5-HT system were shown to be heritable factors in a multitude of psychopathologies (Gaspar, Cases and Maroteaux, 2003). 5-HT has been associated with pathological traits across diagnosed mental disorders, including depression and anxiety disorder, aggression and impulsivity (Apter et al., 1990). Next to the heritable alterations in 5-HT function, early adversity had been shown to take effect on 5-HT system regulation (Booij, Szyf, et al., 2015). In this respect, the approaches used in the current thesis were aimed to answer, at least in part, some of the most relevant questions, regarding the involvement of the 5-HT system in the aetiology and manifestation of such disorders in rodent models of genetic variation. Animal models represent a valuable tool towards the identification of potential candidate genes and affected pathways, mechanisms and circuitries.
Taken together, research reported in the previous chapters supports a role of 5-HT in modulating the effects of early adversity through epigenetic programming of brain developmental trajectories and, consequently, behaviour. A large body of work has already been focused on specific pathways of developmental programming (Booij, Richard, et al., 2015) and acute 5-HT signalling (Paul and Lowry, 2013; Paul et al., 2014). However, only few studies were focussing on the effects and mechanisms in animals lacking brain 5-HT, which allows the determination of, if and how 5-HT is involved in the observed effects of early adversity, which is making our model uniquely fitted to investigate behavioural disorders that emerge in the context of early adversity. The genetically modified mouse models, used in this thesis allow investigating molecular and neuronal correlates associated with altered brain 5-HT system functioning and allows to compare the effects of MS in wildtype animals and mice with an altered 5-HT system. Furthermore, in light of the previously described importance of 5-HT signalling throughout development and its involvement in manifold disorders of the mind, the current study provides a valuable tool to identify potential targets for interventional studies. Identifying molecular markers, neural activation and, consequently, affected subpopulations in specific brain regions. The subregions of the brain each fulfil tremendously complex functions that are subject to reciprocal regulation (Bullmore and Sporns, 2009). Each region consists of subregions, which consist of clusters of specific neurons that can be distinguished by co-expression of certain markers, morphology and electrophysiological characteristics (Hale and Lowry, 2011; Asan, Steinke and Lesch, 2013), which stresses the highly distinctive nature of neuronal signalling. Moreover, despite increasing knowledge in all relevant fields of neuroscience, there still is a deep lack in interdisciplinary knowledge utilisation, which deprives the research community of a wholistic view. Nevertheless, the complexity and comprehensive nature of the involvement of 5-HT in all aspects of an individual’s health, brain circuitry and even gene expression regulation becomes more and more apparent, underscoring an ambiguous role of 5-HT, dependent on time and region of exposure/regulation (Gaspar, Cases and Maroteaux, 2003). Current treatments, however, usually target factors unspecifically over the whole organism. One impressive example of such untargeted approaches is the class of selective serotonin reuptake inhibitors (SSRIs). Components of the family of SSRIs target the 5-HT transporter and, in the brain alone, cause a multitude of effects through prolonged dwelling time within the synaptic cleft and, consequently, increased exposure of 5-HT receptors to their substrate (Ferguson, 2001). Amongst the observed side effects are: sexual dysfunction, weight gain, and sleep problems. Furthermore, more often than not, those treatments are ignorant of effects of genetic variation on the treatment. For example, SSRI side effects were associated with genetic polymorphisms in the 5-HT transporter and receptors (Garfield et al., 2014) as well as for example effects of genetic variations on metabolism of the administered drug (Probst-Schendzielorz, Viviani and Stingl, 2015). Side effects like this are making a more targeted approach preferable to unspecific blockage or activation. In addition, serotonin signalling might represent the consequence and not the cause of neurological alterations, leading to mental disorder (Nordquist and Oreland, 2010), making research on developmental processes, and how genetic alterations and early adversity interfere with such trajectories, vital for the successful determination of acute targets.

To unravel the involved mechanisms in specific brain regions and the physiological consequences of such alterations would finally allow a purposeful intervention, minimising side effects. The work in this thesis addressed the question of gene-by-environment interaction effects on the activation of fear
circuitry as well as expression and expression regulation on a genome-wide level. In the course of this work we identified the amygdala as important hub of early adversity, which interacts with hind brain regions in a 5-HT-dependent manner, regulating behaviour. Moreover, gene expression in limbic brain regions was found to be regulated by early adversity, dependent on 5-HT, and several specific candidate genes were discovered in genome-wide approaches. Thus, the work conducted in this thesis represents a hypothesis-generating approach, pointing out several lines along which future research can develop. Target-specific manipulations in animals, using techniques, such as optogenetic gene activation or inhibition, or stimulation of specific subpopulations of neurons, or genetic as well as epigenetic editing will represent some of the next steps on the way towards more sophisticated approaches to treat mental disorder. Taken together these findings may lead to interventional strategies on the molecular level and to help guiding more invasive therapies, such as deep brain stimulation fitted for the individual patient based on their molecular make-up.


