Neuroscience and Biobehavioral Reviews 72 (2017) 190–209

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

An integrative review of methylation at the serotonin transporter gene and its dialogue with environmental risk factors, psychopathology and 5-HTTLPR

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ARTICLE INFO

Article history:
Received 21 June 2016
Received in revised form 4 November 2016
Accepted 6 November 2016
Available online 20 November 2016

Keywords:
DNA methylation
SLC6A4 gene
5-HTTLPR
G × E interaction

ABSTRACT

Gene—environment (G × E) interactions have largely been regarded as the root of many complex disorders, including several psychiatric disorders. In this regard, it has been hypothesized that epigenetic mechanisms may be the main mediators of such interactions. Of particular interest is the previously described interaction between psychosocial stress and genetic variability of the serotonin transporter gene (*SLC6A4*) in its polymorphic region 5-HTTLPR. Here we review the literature concerning *SLC6A4* methylation in association with environmental, clinical or genetic variables. While *SLC6A4* hypermethylation has typically been described to be independently associated with both early life stress and depressive disorders, only a few papers address whether methylation could mediate the interaction between stress and 5-HTTLPR in predicting psychopathological risk. Nevertheless, research preliminarily indicates a methylation-driven increased vulnerability of carriers of the short allele of 5-HTTLPR to psychiatric disorders when exposed to early stress or soon after exposure to stress.

Contents

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http://dx.doi.org/10.1016/j.neubiorev.2016.11.011
0149-7634/

1. A serotoninergic story

5-Hydroxytryptamine (5-HT), also known as serotonin, is a key neurotransmitter involved in several brain processes such as mood regulation, memory consolidation, aggression and stress response. Nevertheless, its range of action is not limited to the central nervous system (CNS) but expands to cardiovascular and gastrointestinal systems, among others (Berger et al., 2009). In fact, 90% of total serotonin in the organism is stored at enterochromaffin cells, located in the gastrointestinal tract (Gershon, 2004).

In the mid-twentieth century, a serotonergic deficit was postulated as the causative agent of depression thus giving rise to the so-called monoaminergic hypothesis of depression. Soon thereafter, selective serotonin reuptake inhibitors (SSRI) were developed in order to treat depression and, nowadays, they continue to be the first-choice pharmacological treatment for this disorder (Millan et al., 2015). Serotonin was also hypothesized to play a role in the etiology of other psychiatric conditions such as anxiety disorders and schizophrenia (Geyer and Vollenweider, 2008; Graeff, 2002).

As their name indicates, SSRIs act by inhibiting the serotonin transporter, 5-HTT or SERT, which reuptakes secreted 5-HT from the synaptic cleft and returns it to the presynaptic neuron. Thus, SERT became a target not only of drug development, but also of genetic and pharmacogenetic research (Arias et al., 2003). In this regard, the *SLC6A4* gene, which codes for 5-HTT, has been extensively studied, with special interest paid to its promoter-located linked polymorphic region also known as 5-HTTLPR. Functional polymorphism in this region consisting of an insertion/deletion has two major variants: the short (*s*) and the long (*l*) alleles; with the *s* allele being the less active variant that leads to decreased mRNA expression and reduced serotonin clearance at the synaptic cleft (Heils et al., 1996; Lesch et al., 1996). The *s* allele was thus hypothesized to confer risk for a number of psychiatric conditions, including mood disorders, obsessive-compulsive disorder and suicidal tendencies, among others, with the notable exception of schizophrenia (Serretti et al., 2006, 2002). Intriguingly, the *s* allele is often seen as a putative risk allele for a range of psychiatric disorders, although its associated decreased SERT expression would seem to mimic the effect of SSRI-based antidepressant therapy (which blocks this transporter). However, pharmacogenetic studies suggest that carrying the *s* allele is a predictor of worse antidepressant response since the pharmacologic target of SSRIs is already under-expressed. Hence, 5-HTTLPR was also studied in connection with antidepressant response, leading to controversial results (Porcelli et al., 2012; Taylor et al., 2010). From an epidemiological point of view, this polymorphism is relevant due to the high prevalence of both alleles, with an estimated occurrence of the *s* allele around 42% in Caucasian populations (Murphy and Moya, 2011; Serretti et al., 2007).

Caspi et al. shed some light on this conundrum by revealing an insightful gene—environment (G × E) interaction by means of a large longitudinal study in 847 subjects where they observed that the increased depression risk conferred by the *s* allele was only observed in subjects exposed to psychosocial stress if they had distally experienced childhood maltreatment or they reported proximal stressful life events (Caspi et al., 2003). Several meta-analyses have since been published once again leading to conflicting interpretations of the literature: while some papers support the unprecedented results described by Caspi et al. (Sharpley et al., 2014), others find no evidence of a G × E interaction between 5-HTTLPR and exposure to stress in mediating depression liability, arguing that the observed associations are likely to be statistical artifacts (Munafò et al., 2009; Risch et al., 2009). Moreover, the aforementioned phenotypic effects of 5-HTTLPR have been suggested to operate by means of abnormal brain functioning. Briefly, *s* carriers exhibit heightened amygdala reactivity to environmental threat compared to *l* homozygotes, which could be a risk endophenotype for developing stress-related disorders after exposure to stressful experiences (Munafò et al., 2008). Hence, the next step was to explore the mechanisms that could be mediating this interaction; thereby providing a more complex framework that would explain the conflicting results.

Epigenetic mechanisms, defined as any process that alters gene expression without changing the DNA sequence, have been hypothesized to be responsible for embedding contextual cues and thus mediating the biological impact of the environment on an exposed individual (Petronis, 2010). DNA methylation is one of the epigenetic modifications that has received most attention from the scientific community due to the methodological ease with which it can be studied and the balance between stability and reversibility of methylation markers. Generally, DNA methylation occurs in cytosines that are adjacent to guanines forming the so-called CpG sites; although, it has recently been reported that DNA methylation can also occur in non-CpG cytosines. Interestingly, although CpG sites can be found isolated within or between genes, they tend to cluster in the promoter regions of genes; these clusters of CpG sites are known as CpG islands. CpG islands are naturally unmethylated, which has been associated with high expression levels by research in several fields. Briefly, methylation at GC-rich DNA fragments increases DNA attraction and thus alters chromatin accessibility (Yoo et al., 2016). Conversely, methylation at CpG sites located in CpG island shores or intragenic regions seems to be associated with higher rather than lower expression, although the underlying mechanisms are still under discussion (Ball et al., 2009; Edgar et al., 2014).

In the particular case of SERT, variability at both *SLC6A4* methylation and 5-HTTLPR have independently been associated with changes in *SLC6A4* expression: specifically, higher methylation and