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REVIEW

DNA METHYLATION AND CHILDHOOD MALTREATMENT: FROM ANIMAL MODELS TO HUMAN STUDIES

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Abstract—Childhood maltreatment (CM) has estimated prevalence among Western societies between 10% and 15%. As CM associates with increased risk of several psychiatric disorders, early age of illness onset, increased comorbidity and negative clinical outcome, it imposes a major public health, social and economic impact. Although the clinical consequences of CM are well characterized, a major challenge remains to understand how negative early-life events can affect brain function over extended periods of time. We review here both animal and human studies indicating that the epigenetic mechanism of DNA methylation is a crucial mediator of early-life experiences, thereby maintaining life-long neurobiological sequelae of CM, and strongly determining psychopathological risk.

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Key words: childhood maltreatment, maternal care, epigenetic, DNA methylation, glucocorticoid receptor, stress.

Contents

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Abbreviations: 5-hmC, hydroxyl–methyl–cytosine; BDNF, brain-derived neurotrophic factor; CM, childhood maltreatment; DNMT, DNA methyltransferase; GR, glucocorticoid receptor; HPA, hypothalamic–pituitary–adrenal; IVF, *in vitro* fertilization; KO, knockout; LG, licking and grooming; MBD, methyl-binding proteins; MeCP2, methyl-CpG-binding protein 2; MSUS, unpredictable maternal separation combined with unpredictable maternal stress; PTSD, post-traumatic stress disorder; PVN, paraventricular nucleus; TSS, transcription start site.

INTRODUCTION

Childhood maltreatment (CM) is a global problem of significant proportion that affects children of all ages, race, economic, and cultural backgrounds (Gilbert et al., 2009; Green et al., 2010; McLaughlin et al., 2010b). There are four main types of childhood maltreatment: sexual abuse, physical abuse, psychological abuse and parental neglect. In addition, other forms of early-life adversity have been studied in humans, including witnessing parental violence, rearing in orphanage or severe parental psychopathology (Lupien et al., 2000; Essex et al., 2002; Halligan et al., 2007). While obtaining reliable estimates of the prevalence of childhood maltreatment is challenging, community studies suggest rates for all forms of maltreatment averaging around 10% to 15% (Kessler et al., 1997; Holmes and Slap, 1998; Edwards et al., 2003; Gilbert et al., 2009).

There exists a strong relationship between CM and negative mental health outcomes (Mullen et al., 1996; Collishaw et al., 2007; McLaughlin et al., 2010b). Maltreatment during early development is among the strongest predictors of psychiatric pathology and severity of the clinical course, including early onset of illness, poor treatment response, increased comorbidity and chronic health care utilization (Kessler et al., 1997; Widom, 1999; Lansford et al., 2002; Edwards et al., 2003; Ystgaard et al., 2004; Evans et al., 2005; Collishaw et al., 2007; Widom et al., 2007a,b,c; Afifi et al., 2008; Gilbert et al., 2009; McLaughlin et al., 2010a). It is strongly associated during adulthood with obesity, personality disorders, depression, substance use disorders, aggressive and violent behaviors (Widom, 1989; Zingraff et al., 1993; Smith and Thornberry, 1995; Magdol et al., 1998; Stouthamer-Loeber et al., 2001; Thornberry et al., 2001; Bevan and Higgins, 2002; Fagan, 2005; Loeber et al., 2005; Lansford et al., 2007), as well as suicidal behaviors (Brezo et al., 2008; Fergusson et al., 2008; Wanner et al., 2012). In comparison, the association of CM with psychosis appears weaker (Gilbert et al., 2009).

Close family members are the main source of support during development and are essential to provide healthy attachment patterns, appropriate emotional regulation to environmental stimuli, and stress resilience (Malatesta, 1988; Cole et al., 1994). Therefore, the experience of repetitive acts of abuse by parental figures, caregivers

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or other close relatives signals a hostile and unreliable environment that may trigger brain adaptations in key response systems. These changes may then induce the development of personality and cognitive traits, which in turn increase the risk of psychopathology (Turecki et al., 2012). Epigenetic processes are now emerging as crucial mediators of such long-term biological embedding of CM (Turecki et al., 2012; Hertzman, 2012).

Epigenetics refers to the collective chemical and physical processes that program the genome to express its genes in a time- and cell-dependent manner. These mechanisms are capable of conveying information through meiotic and mitotic divisions in the absence of a change in the DNA sequence. The epigenome is responsive to developmental, physiological and environmental cues. As such, epigenetics explains how the environment regulates the genome, and are well suited to mediate the effects of early environmental factors, potentially throughout the lifespan. Epigenetics includes post-translational modifications of histone proteins (the core components of chromatin, see reviews by Hooker and colleagues, and Akbarian and colleagues, in this *Neuroscience* special issue), non-coding RNAs (most notably micro-RNAs), and DNA methylation. The present review will focus on DNA methylation, the epigenetic mark that received by far the most interest in the field of CM.

Overall, the plethora of adverse mental health consequences associated with the experience of CM strongly suggests the involvement of several neurotransmitter systems and brain regions. In addition, complementary human and animal studies clearly indicate that negative early-life experiences affect homologous neurobiological substrates across species, potentially through similar epigenetic mechanisms. Therefore, we will discuss here both animal models and human studies of CM. In rodents, several groups have now reported convincing evidence for the crucial role of the epigenetic processes in mediating maladaptive neurobiological and behavioral consequences of the early-life environment and environmental adversity. In humans, studies of brain postmortem tissues have started unraveling epigenetic alterations associated with CM, which strikingly resemble previous animal findings. Hopefully, studying CM-induced DNA methylation changes in peripheral tissues of living subjects may lead in the future to the identification of epigenetic biomarkers, with potentially major clinical implications.

DNA METHYLATION: A MAJOR EPIGENETIC ACTOR

DNA methylation refers to the covalent addition of a methyl group in position 5′ to a cytosine residue (5-mC), in particular when a cytosine is followed by a guanine (CpG dinucleotide). DNA methylation at sequences other than CpG, as well as other chemical modifications of the DNA molecule (such as 5-formyl-cytosine or 5-carboxy-cytosine), have been described (Lister et al., 2009; Yu et al., 2012; Varley et al., 2013) but will not be discussed further: their abundance in mammalian genomes is low (Ito et al., 2011), in particular in somatic cells (Ziller et al., 2011); the dynamics and functional impact of these marks only begins to be appreciated (Shen et al., 2013; Song et al., 2013), and their potential role in behavioral phenotypes such as those associated with CM has yet to be studied.

DNA methylation is controlled by a family of DNA methyl-transferase proteins (DNMT). DNMT1, DNMT3A and DNMT3B all three contribute to the maintenance of DNA methylation patterns through mitotic divisions, while DNMT3A and DNMT3B are responsible for the acquisition of *de novo* methylation (Jones, 2012). Active mechanisms of DNA demethylation have long remained controversial, but are now clearly documented, notably through excision base repair processes, or the conversion to 5-hydroxyl–methyl–cytosine (5-hmC) (Kriaucionis and Heintz, 2009). As will be discussed below, both DNA methylation and demethylation mechanisms are likely recruited by early-life unfavorable experiences.

Around 70–80% of CpGs are methylated in the genome (see Hoffmann and Spengler (2012) in this special issue, and Jones (2012)). This epigenetic mark globally associates with decreased transcriptional activity (Jones, 2012), and the strength of this general rule has been recently confirmed in the brain at the genome-wide level (Labonte et al., 2012a), although there are documented exceptions (such as the corticotropin releasing hormone receptor type 2, CRH-R2 gene, see below). Most work on DNA methylation has focused on CpG islands, which are defined (although this is debated Illingworth and Bird (2009)) as short, 1-kb CpG-rich regions that are present in roughly half of the genes in vertebrate genomes. CpG islands are overrepresented in promoter regions, where methylation levels are very low, leaving surrounding DNA and transcription start site unwrapped and accessible for transcription. The functional implications of DNA methylation in other genomic regions (‘‘shores’’ of CpG islands, gene bodies, intergenic regions) remain comparatively less understood. CpG methylation in gene bodies, in contrast with promoter regions, was initially associated with increased transcription in B-lymphocytes and fibroblasts (Ball et al., 2009; Lister et al., 2009). However, most recent data reveal a neuron-specific negative correlation between gene bodies CpG methylation states and gene expression (Guo et al., 2011a; Mellen et al., 2012), suggesting epigenetic regulatory mechanisms specific to the brain tissue.

In the context of CM, most available studies correlate DNA methylation states with gene expression levels, potentially implicating several mechanisms. First, the methylation of certain CpG dinucleotides, notably in gene promoter regions, impairs the ability of regulatory proteins (such as transcription factors) to bind the DNA and to promote gene expression (see below a prototypical example with the glucocorticoid receptor (GR) gene promoter). Second, several proteins have been shown to specifically bind methylated DNA. This family of methyl-binding proteins (MBD) includes methyl-