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Review

Epigenetics and migraine; complex mitochondrial interactions contributing to disease susceptibility

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ABSTRACT

Migraine is a common neurological disorder classified by the World Health Organisation (WHO) as one of the top twenty most debilitating diseases in the developed world. Current therapies are only effective for a proportion of sufferers and new therapeutic targets are desperately needed to alleviate this burden. Recently the role of epigenetics in the development of many complex diseases including migraine has become an emerging topic. By understanding the importance of acetylation, methylation and other epigenetic modifications, it then follows that this modification process is a potential target to manipulate epigenetic status with the goal of treating disease. Bisulphite sequencing and methylated DNA immunoprecipitation have been used to demonstrate the presence of methylated cytosines in the human D-loop of mitochondrial DNA (mtDNA), proving that the mitochondrial genome is methylated. For the first time, it has been shown that there is a difference in mtDNA epigenetic status between healthy controls and those with disease, especially for neurodegenerative and age related conditions. Given co-morbidities with migraine and the suggestive link between mitochondrial dysfunction and the lowered threshold for triggering a migraine attack, mitochondrial methylation may be a new avenue to pursue. Creative thinking and new approaches are needed to solve complex problems and a systems biology approach, where multiple layers of information are integrated is becoming more important in complex disease modelling.

Contents

Abbreviations: WHO, World Health Organisation; mtDNA, mitochondrial DNA; MA, migraine with aura; MO, migraine without aura; CSD, cortical spreading depression; GWAS, Genome Wide Association Study; HDACs, histone deacetylases.

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1. Introduction

Migraine is a common neurological disorder characterised by severe head pain and an assortment of additional symptoms which can include nausea, photophobia, phonophobia and for some subtypes of migraine additional neurological symptoms. Migraine is classified according to the International Headache Society into two broad categories namely migraine without aura (MO) and migraine with aura (MA) (Eriksen et al., 2004; Olesen and Lipton, 1994). Most patients suffer from MO, with only 20% of sufferers experiencing an aura before the onset of a migraine attack. Approximately 12% of the Caucasian population suffers from this debilitating disease with almost 2/3 of sufferers being female. Migraine is classified by the World Health Organisation (WHO) as one of the top twenty most debilitating diseases in the developed world and poses a significant personal and economic burden (Leonardi et al., 2005).

In 2010 it was estimated that headache disorders in Europe cost an estimated €43.5 billion per year (Gustavsson et al., 2011). It has been shown that the cost incurred by continuous absenteeism from the work place as a result of employees being unable to work due to debilitating migraine attacks is actually higher than the direct cost of treatment. Also the total percentage of costs attributed to loss of work place productivity caused by chronic disease is by far dominated by migraine with 89% attributed to migraine and only 19% for other chronic conditions (Schultz et al., 2009). Current therapies are only effective for a proportion of sufferers and new therapeutic targets are desperately needed to alleviate this burden.

Various theories explaining the pathophysiology of migraine have been tested and modified for the last eight decades. The most supported current view is that migraine is a complex multifactorial disease with both predisposing genetic variance and environmental factors contributing to the final phenotype. The actual biological mechanism involved in a migraine attack is still debated, but is thought to be caused by activation of the trigeminal nerve causing pain sensation in the sensor cortex of the brain and/or a dysfunction of the neuronal nuclei located within the brain stem (Ho et al., 2010). The trigeminal vascular theory states that activation of the trigeminal nerve system by a neural, vascular or neurovascular trigger leads to a migraine. The trigeminal nerves carry pain signals from the meninges and blood vessels infusing the meninges to the trigeminal nucleus in the brain stem which in turn sends signals to the sensor cortex via the thalamus. The sensor cortex processes pain signals and other senses, thus leading to the sensation of pain experienced during migraine attacks (Oshinsky and Luo, 2006). This mechanism is illustrated in Fig. 1 below.

Dysfunction of neuronal nuclei can be explained by migraine pain and trigeminovascular activation being caused by a central mechanism which may not require a primary sensory input (Goadsby and Akerman, 2012; Lambert et al., 2011). The most recent theory explaining migraine pathogenesis describes migraine as a dysfunction of the subcortical brain structures including the brainstem and diencephalic nuclei which are involved in modulating sensory inputs. The theory suggests that aura is triggered by dysfunction of these nuclei and that the same mechanism is responsible for the pain and other symptoms experienced during migraine attacks (Akerman et al., 2011). This theory challenges the importance of cortical spreading depression (CSD) in generating a migraine attack, a process which has previously been emphasized. CSD is a wave of neuronal and glial depolarization/neuronal hyperexcitability followed by a long lasting suppression of neural activity (de Almeida et al., 2009). This electrophysiological event has been linked to aura in the human visual cortex and is thought to be partly responsible for the sensory and motor disturbances experienced during MA attacks.

2. Heritability and migraine: a significant genetic contribution

Heritability is the proportion of a trait or disease phenotype which can be attributed to genetic variation. The official definition of heritability is the "proportion of phenotypic variation (V_P) that is due to variation in genetic values (V_G)." Genetic values (V_G) include the combined effect of all loci as well as interactions within (dominance) and between (epistasis) loci. Two different basic heritability values can be calculated namely broad-sense and narrow-sense heritability. Broad-sense heritability, or H^2 is defined as the proportion of phenotypic variation due to genetic values which include effects of dominance and epistasis ($H^2 = V_G / V_P$) while narrow-sense heritability only considers genetic variation due to additive genetic values ($h^2 = V_A / V_P$) (Hill et al., 2004).

For human diseases and other complex traits, heritability can be estimated from the concordance rate between monozygotic and dizygotic twins (Macgregor et al., 2006). More complex models which examine

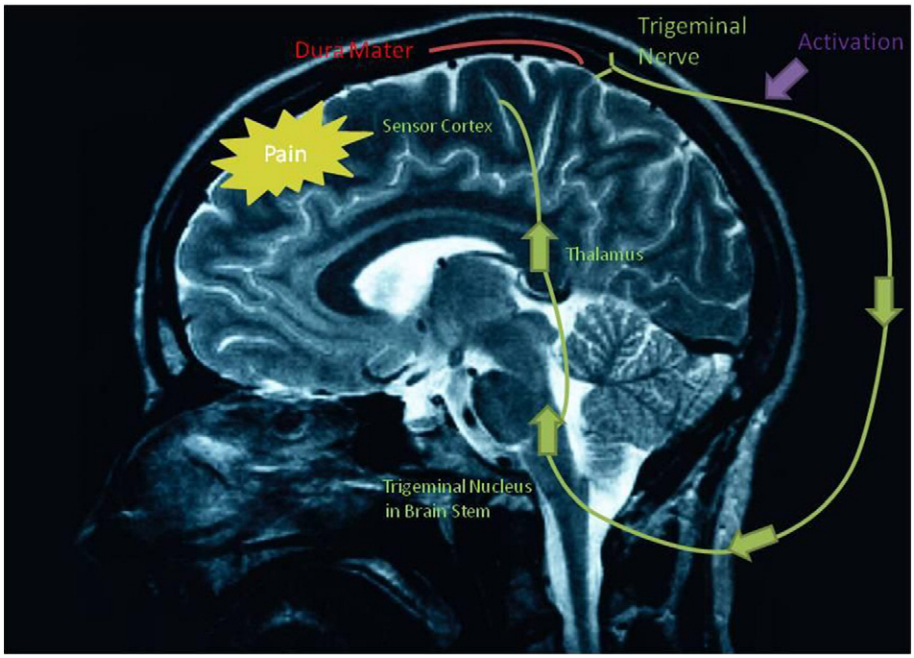

Fig. 1. Upon activation of the trigeminal nerve, pain signals are carried to the trigeminal nucleus and then to the sensor cortex via the thalamus.