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Review

Mitochondria and the economy of stress (mal)adaptation

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ABSTRACT

Stress-associated diseases, like depression have a life time prevalence of up to 20%, and approximately 18.4 million people in Europe suffer from depression. Despite decades of research, we still do not understand completely this complex brain disease. Increasing body of correlative evidence implicates mitochondria in the aetiology of depression, but the fundamental question of how suboptimal mitochondrial function causes depression remains to be answered. Here we propose that the balance between cost of adaptation to our ever changing environment (*stress*) and available energy (*mitochondrial function*) is crucial for mental health. More specifically, stress activates the brain, and changes its structure and function (*neuronal plasticity*). This comes at a metabolic cost that is primarily met by energy produced by mitochondria. Individuals with optimal mitochondrial function could meet critical energy demands of stress-induced neuronal-plasticity, thus are at relatively low risk for depression. In contrast, in individuals with suboptimal mitochondrial function stress-associated depletion of the brain's energy resources could ultimately compromise neuronal plasticity that in-time could render an individual vulnerable for depression. Naturally, this does not imply that all mitochondrial patients suffer from depression, or that all depressed patients have underlying mitochondrial pathology. It, however, does imply that suboptimal mitochondrial function could be pathogenic in a subgroup of patients with depression. If so, this will not only have a profound effect on our understanding of depression, but on therapy and counselling, that will also be discussed.

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1. Unmet need

One in five individuals will have a depression at some point in life and approximately 10% of the population suffers from depression at any one time (Kessler et al., 2003; Lopez and Murray, 1998; Pincus and Pettit, 2001). To date approximately 18 million people in Europe suffer from depression (Wittchen and Jacobi, 2005; Wittchen et al., 2005), with several hundred thousand people per European countries (Andlin-Sobocki and Wittchen, 2005). The frequency of depression in the general paediatric population is also strikingly high (3–4%), rising throughout adolescence (Kovacs, 2002; Verhulst et al., 1997). Furthermore, it has been estimated by the World Health Organization that depression, by 2020 will be the highest ranking cause of disease. Depression that often becomes chronic has profound effect on the individual, his or her family, and society as a whole. It also is a tremendous social and financial burden in the form of impaired relationships, lost productivity, and wages (Kessler et al., 2003; Lopez and Murray, 1998; Pincus and Pettit, 2001).

Although depression has been associated with multiple aetiologies and pathogenic mechanisms, the understanding of the neurobiology and treatment of this complex disorder remains poor. This notably relates to the clinical heterogeneity and the rather promiscuous aetiology of this disease. Nonetheless, depression is thought to result from molecular and cellular mechanisms that interact with environment (*stress*) and genetic factors, and manifests themselves in defects in neuronal plasticity (Pittenger and Duman, 2008). It is important to recognize too, that many questions still remain regarding disease aetiology, and that in order to determine tomorrow's novel therapeutic avenues for depression, we should look for new concepts, and beyond the classical theories (Gardner and Boles, 2011; Gelenberg, 2010; Joels and Baram, 2009; Krishnan and Nestler, 2008; Martin et al., 2010; Morava et al., 2010; Nestler and Hyman, 2010).

2. Stress response

Adverse life experience or stress is undoubtedly one of the major risk factors for the development of depression (see *e.g.* de Kloet et al., 2005; Holsboer et al., 1984; Joels and Baram, 2009; Kozicz, 2009; McEwen, 2003; Nemeroff and Vale, 2005; Schmidt, 2011). The brain enables coping to daily events as well as to major challenges to maintain stability throughout change (see *e.g.* McEwen, 1998; McEwen and Wingfield, 2003; Selye, 1946; Sterling and Eyer, 1988). This is achieved by a well orchestrated symphony of neuronal and network responses by a plethora of stress mediators in the brain (see *e.g.* Bale and Vale, 2004; de Kloet et al., 2005; Duman and Monteggia, 2006; Duman and Voleti, 2011; Feder et al., 2009; Joels and Baram, 2009; Joels et al., 2008; Kozicz, 2007; Krishnan and Nestler, 2008; Pittenger and Duman, 2008; Price and Drevets, 2012). Stress recruits a variety of biochemical, regulatory, developmental and anatomical processes (we call them "*nodes*"), and depending on the type, duration and severity of the stressor, as well as on the developmental age and sex of the animal, stress recruits one or many of these nodes, which will orchestrate the animals' complex physiological, neuroendocrine and behavioural stress response (see *e.g.* Joels and Baram, 2009; Krishnan and Nestler, 2010; Nestler, 2009). Evidence also highlights the idea that depression is caused by a highly diverse interaction of these nodes, and a way to link them to depression maybe through the notion that alterations in one, or perhaps in several of these nodes confers risk for depression (see *e.g.* Joels and Baram, 2009; Krishnan and Nestler, 2010; Nestler, 2009). However, despite several decades of research that has although identified the significance of these nodes in depression pathophysiology progress in understanding depression has been frustratingly slow. Specifically, mounting evidence points to the fact that the removal of any single node either has no effect, owing to considerable compensatory responses by other nodes, or, only marginal alterations in the animal's stress response can be seen, and most importantly, none of them seem to be exclusively responsible for the aetiology of depression in general (see *e.g.* Bale and Vale, 2004; de Kloet et al., 2005; Deakin, 1998; Duman and Monteggia, 2006; Duman and Voleti, 2011; Feder et al., 2009; Graeff et al., 1996; Homberg and Lesch, 2011; Joels and Baram, 2009; Krishnan and Nestler, 2008; McEwen, 2007; Nemeroff, 1988; Nestler, 2009; Pittenger and Duman, 2008; Price and Drevets, 2012; Reul and Holsboer, 2002). Two phenomena, however, are common to all of these stress-sensitive neuronal networks; *i.e.* they all show considerable stress-induced neuronal plasticity (see *e.g.* Bale, 2006; Bale and Vale, 2004; Belmaker and Agam, 2008; de Kloet et al., 2005; Dumas et al., 2010; Joels and Baram, 2009; Krishnan and Nestler, 2008; McEwen, 2007; McEwen et al., 2011; Miklos and Kovacs, 2012; Nederhof and Schmidt, 2012; Nestler, 2009; Pittenger and Duman, 2008; Price and Drevets, 2012; Reul and Holsboer, 2002), as well as remarkable individual variations (*e.g.* Elliott et al., 2010; Krishnan et al., 2007; Schmidt et al., 2007, 2008). More specifically, applying paradigms of chronic social defeat or social stress, resilient and susceptible individuals can be identified (Elliott et al., 2010; Krishnan et al., 2007; Schmidt et al., 2007), and like humans, rodents prone to develop a depression-like phenotype represent 15–20% of the total population (Schmidt, 2011; Wittchen and Jacobi, 2005; Wittchen et al., 2005). In addition, rodent studies have also supported the role of individual differences in coping and problem solving strategies in the aetiology of depression (Liu and Alloy, 2010).

2.1. But what can be the explanation for such individual differences in stress-vulnerability?

Stress-related alterations in the structure and function of stress-sensitive nodes require sufficient energy mobilization and come at a considerable metabolic cost, leading to a strong energy demand that is primarily met by mitochondria (DiMauro et al., 2001; DiMauro and Schon, 2008; Herculano-Houzel, 2011). In this process, the critical energy demand and optimal mitochondrial function need to be balanced. Therefore, we propose that individual differences in mitochondrial function (efficiency of oxidative phosphorylation) could explain vulnerability or resilience to stress-related pathophysiology. Hence, in individuals with suboptimal mitochondrial function, adverse life events may rapidly exhaust energy reserves, thereby compromising stress-associated neuronal plasticity. In time, the result can manifest itself in depression. Such a suboptimal mitochondrial function could be the results of genetic factors in the form of primary mitochondrial disorders, but also due to stress-related exhaustion (Fig. 1). Furthermore, implicit in the concept of suboptimal mitochondrial function is the idea that processes that promote and/or result from stress alter mitochondrial function, thereby facilitating the