Neuroscience and Biobehavioral Reviews 32 (2008) 1103–1120

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review

What do we know about the long-term consequences of stress on ageing and the progression of age-related neurodegenerative disorders?

Marie-Christine Pardon *, Ivan Rattray

Institute of Neuroscience, School of Biomedical Sciences, University of Nottingham Medical School, Queen's Medical Centre, Nottingham NG7 2UH, United Kingdom

ARTICLE INFO

Keywords:
Environmental stress
Ageing
Alzheimer's disease
HPA axis
Behaviour
Cognition

ABSTRACT

The aim of this paper is to review evidences that stressful events throughout life can have a long-term impact on ageing and the progression of Alzheimer's disease. As early as the prenatal or neonatal period, stress can alter the rate of cognitive decline and neurodegenerative changes in the brain in a stressor-dependent manner, with prenatal restraint and maternal separation usually causing damage to the brain, whereas neonatal handling was found protective. The occurrence of negative outcomes of early stress can, however, be reversed by subsequent events known to be beneficial to the ageing process. After the early developmental period, it is currently unknown how stress will impact on the ageing process, due to a lack of studies. On the other hand, there is evidence of a lack of plasticity of the brain monoaminergic systems in response to stress with age, and of age-dependent changes in the immediate impact of stress, which is greater in subjects vulnerable to age-related cognitive decline. In addition, vulnerability to stress enhances the risk of developing Alzheimer's disease in humans and chronic substantial stress in animal models of the disease accelerates both the onset and progression of pathological markers in the brain. In an attempt to integrate these findings, a hypothesis is presented here whereby stress, in susceptible individuals, would precipitate age-related cognitive decline and hippocampal integrity during normal and pathological ageing, but will only affect the progression of pathological markers of Alzheimer's disease in the presence of other risk factors to this neuropathological disorder.

Contents

1. Introduction: stress, ageing and Alzheimer's disease . . . 1104
2. The hypothalamo-pituitary–adrenal (HPA) axis and its changes during normal and pathological ageing . . . 1104
3. The long-term impact of stress on normal ageing . . . 1105
   3.1. The consequences of early environmental stress on ageing . . . 1105
      3.1.1. Prenatal stress . . . 1105
      3.1.2. Neonatal and early postnatal stress . . . 1107
      3.1.3. Juvenile-adolescence stress . . . 1108
      3.1.4. Summary . . . 1108
   3.2. Adulthood to senescence stress and ageing . . . 1108
4. The impact of stress on the progression of Alzheimer's disease . . . 1111
   4.1. Clinical studies . . . 1111
   4.2. Preclinical studies in animal models of Alzheimer's disease . . . 1112
   4.3. Stress and sporadic Alzheimer's disease . . . 1115
   4.4. Summary . . . 1116
5. Potential mechanisms linking stress, ageing and Alzheimer's disease . . . 1116
6. Conclusions . . . 1118
   Acknowledgements . . . 1118
   References . . . 1118

* Corresponding author. Tel.: +44 115 82 30157; fax: +44 115 82 30142.
E-mail address: marie.pardon@nottingham.ac.uk (M.-C. Pardon).
URL: http://www.nottingham.ac.uk/neuroscience/contact/a-z/M-R/pardon_marie.phtml

0149-7634/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neubiorev.2008.03.005

1. Introduction: stress, ageing and Alzheimer's disease

A large body of evidence has established that stress can have adverse consequences on brain function and, as such, can lead to a range of mental disorders. Most of the clinical and preclinical studies in this area have focused on the outcomes of stressful challenges during development and in adulthood. A negative impact of stress on the ageing process and the progression of related neurodegenerative diseases is also suspected but far from being well appreciated. With the increased human life expectancy, the demands on the public health system and on medical and social services show considerable increases. Similarly, stress-related disorders constitute a major economic burden and health issue in modern societies as a consequence of the increasing pressure imposed to individuals, particularly in the work place (IRS Survey, 2007). Thus, it is essential to understand how stress can later impact on mental health during ageing to improve quality of life, care and treatment of elderly people.

Many difficulties are expected in this respect given the complex relationship between ageing and stress, which has been reviewed elsewhere (Pardon, 2007). In brief: (1) life expectancy and the quality of the ageing process are genetically determined by those genes involved in tolerance to stress, (2) this stress resistance potential is, however, modulated by both the amount of stress experience and age, and (3) stress and ageing mimic each other but interact in a sometimes, paradoxical way with stress being able to either relieve or exacerbate the ageing process and similarly ageing can cause stress to have a stronger or weaker impact, and these interactive effects remain a mystery (Pardon, 2007). In this context, it is difficult to predict how stress will later impact on mental health during ageing since the circumstances in which life will then follow its course act as a stochastic process that will constantly alter predictions.

The primary objective of this paper is to review the literature dealing with the long-term consequences of stress on mental function in the elderly in an attempt to identify the factors modulating its impact and the potential underlying mechanisms. However, due to a lack of studies investigating the repercussion of stress exposure during the post-developmental period on senescent cognitive functioning, we will also review the rare studies that have looked at the consequences of stress exposure from midlife and discuss the potential long-term impact. In addition, particular attention will be allocated to the involvement of stress in the onset and progression of Alzheimer's disease (AD) which is emerging from recent literature. Here, we will investigate whether this neurodegenerative disorder is a long-term consequence of stress exposure.

After a brief introduction of the stress response and its changes with ageing and AD, the second part of the review will deal specifically with the long-term impact of early stress applied during the developmental period on adaptive mechanisms and mental functions later in life. The third part of the review will deal with the immediate consequences of stress applied from midlife, and finally, the last part will review the recent literature demonstrating a role of stress systems in the onset and progression of AD. We will then attempt to integrate these findings to identify potential mechanisms underlying the long-term consequences of stress on ageing and related brain disorders.

2. The hypothalamo-pituitary–adrenal (HPA) axis and its changes during normal and pathological ageing

The HPA axis is one of the primary effectors of the stress response in mammals, allowing the organism to adapt to changes to its internal or external environment. The stress response has been widely described in other reviews (Johnson et al., 1992; Bao et al., 2008) and involves central and peripheral changes coordinated by the central nervous system. The release of glucocorticoids (GCs: cortisol in humans, corticosterone in rodents), the main stress hormone, is controlled by the paraventricular nucleus of the hypothalamus, where parvocellular neurons synthesise and release corticotropin-releasing hormone (CRH) in response to the stress. These neurons also secrete other hormones, such as arginine vasopressin, which act synergistically with CRH to drive the activation of the HPA axis. The release of CRH into the pituitary portal system causes the release of adrenocorticotropic hormone (ACTH) from the pituitary which, in turn, causes the release of GCs from the adrenal cortex. GCs act back on the hypothalamus and pituitary (to suppress CRH and ACTH production) in a negative-feedback cycle to terminate the stress response after the threat has passed, thereby preventing excessive responses which would lead to pathological conditions. GCs play a vital role in regulating many aspects of the stress response. Together with other stress-sensitive systems (e.g., the sympathetic-adrenomedullary system), GCs prepare the body for adaptation by mobilising energy stores, suppressing nonessential physiological systems (e.g., feeding, reproduction), and orchestrating behavioural responses to stimuli perceived as stressful.

In the brain and other organs, GCs act through two types of receptors: the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). MR expression is almost exclusively restricted to the hippocampus, a brain structure involved in learning and memory processes, where they mediate tonic influences of GC on hippocampus-dependent function, although they are also found in the hypothalamus and amygdala. Conversely, GRs are widely expressed throughout the brain with high density in regions such the hippocampus, amygdala and prefrontal cortex, where they mediate the feedback action of GCs on stress-activated brain processes (Reul and de Kloet, 1985, 1986).

Changes in the HPA axis with normal and pathological ageing have also been extensively reviewed elsewhere (Meaney et al., 1995; Pedersen et al., 2001; Lupien et al., 2005; Swaab et al., 2005; Bao et al., 2008; Pardon, 2007). To summarise, the level of GRs and MRs decline with age, contributing to impaired regulation of the HPA axis, and altered stress responses. However, while, this is expected to lead to impaired negative feedback of the HPA axis and, as such, enhanced basal levels of GCs, hippocampal atrophy and cognitive dysfunction, it has been found in both humans, and rodents, that hypercortisolemia is not a consistent feature of ageing, but rather a feature associated with accelerated age-related cognitive decline (reviewed in Meaney et al., 1995; Lupien et al., 2005; Pardon, 2007), although hypercortisolemia is rather mild in AD patients despite the profound cognitive decline (Swaab et al., 2005; Bao et al., 2008). Furthermore, the expression of both GCs receptor types was not reduced in the hippocampus of AD patients in comparison to age-matched control subjects (Seckl et al., 1993; Wetzel et al., 1995). Such changes, however, have a greater influence on the ability to respond to stress, and are associated with an impaired ability to terminate the stress response, leading to enhanced vulnerability to adverse effects of stress (Meaney et al., 1995). Additionally, it has been suggested that hippocampal neuron loss and associated cognitive decline result from a combination of sustained basal GC levels and stress (Pedersen et al., 2001).

It is worth noting that stress does not always have adverse effects, and pathological outcomes are largely the consequences of repeated uncontrollable or inescapable exposures to stressors (for review Joels et al., 2007), but there are a number of reports of improved learning and memory abilities following chronic stress (Bartolomucci et al., 2002; Li et al., 2007; Pardon et al., 2007), and evidence that chronic low level of stress improve