Neuro-endocrinology BRIEFINGS

8

GLUCOCORTICOIDS, AGEING AND NERVE CELL DAMAGE

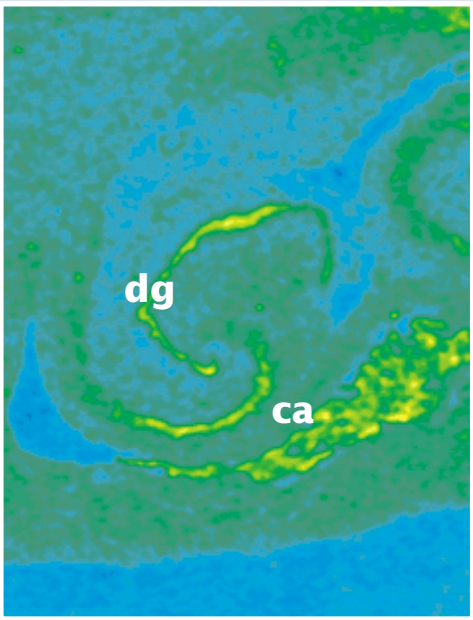
SUMMARY

Stress, by releasing glucocorticoid hormones, affects the brain, especially a region called the hippocampus which has high levels of glucocorticoid receptors. Chronic stress or glucocorticoid oversecretion adversely affects the hippocampus, reducing nerve cell connections and producing memory impairments. The elderly are particularly vulnerable to this degenerative process. What are the events that underlie this important disorder and are there ways to prevent age-related loss of the ability to learn and memorise ?

Expression of glucocorticoid receptor gene in the hippocampus of the human brain. Yellow colours indicate high levels of gene expression in the dentate gyrus (dg) and cornu ammonis (ca) regions of the hippocampal formation.

Hormone cascade

Somehow we know that *stress* is bad for us, particularly for our mental health and well-being. But how does this come about? Recently, a series of studies has suggested that hormones may be the key mediators of the adverse effects of stress on the brain. One of the major consequences of stress, be it physical stress (such as severe illness, trauma or pursuit by a lion) or psychological stress (such as public speaking, bereavement or mental illness), is activation of a region of the brain called the hypothalamus. This triggers a cascade of hormones called the hypothalamic-pituitary-adrenal-axis, leading to the release of glucocorticoid hormones (cortisol, corticosterone) from the adrenal gland which then act upon a variety of tissues. This response is of course crucial in the short term to enable the body to survive stress. Glucocorticoids increase blood pressure and the availability of the body's major metabolic fuels, all the better to escape the physical or psychological threat. At the same time glucocorticoids inhibit non-essential processes, such as inflammation, growth and reproduction. Clearly such matters can be more safely undertaken when escape from the lion or the auditorium has been accomplished! Whilst these responses are beneficial in the short term, with chronic stress and glucocorticoid excess, a series of deleterious effects occur, including myopathy, osteoporosis, hypertension, diabetes, reproductive failure and infections. Unsurprisingly, glucocorticoids also have potent effects on the brain, most notably on the hippocampus, a region critical for learning and memory, as well as being a crucial centre for glucocorticoid feedback inhibition of their own release.



Neuronal endangerment

The hippocampus has the highest density of receptors for glucocorticoids in the brain. Here low levels of glucocorticoids are essential to maintain nerve cell function and survival. In contrast, glucocorticoid

excess interferes with nerve cell function in the hippocampus, interrupting the critical processes in synapses which are thought to underpin learning and memory. Moreover, glucocorticoids also interfere with the uptake of glucose by hippocampal nerve cells, thus making them vulnerable to other insults, such as lack of oxygen, loss of blood supply (stroke) and fits. Such neuronal 'endangerment' has been associated with alterations in the structure of nerve cells so that they lose their critical connections with other nerve cells. Eventually, particularly when other pathological processes such as stroke or ageing intervene, neurones in the hippocampus may die in the presence of excess glucocorticoids.

Loss of memory

Whilst these findings are interesting at a cellular level, do they have any relevance to the intact normal brain? Recently it has become apparent that approximately one third of aged animals and humans develop a syndrome comprising a triad of (i) excess levels of glucocorticoids, (ii) loss of hippocampal learning and memory and (iii) deleterious changes in the structure of hippocampal nerve cells and sometimes neuronal death. The causative role of glucocorticoids in this process was first illustrated more than 20 years ago by experiments in which glucocorticoid levels were maintained low throughout life by removing the adrenal glands. Such treatment largely prevented the emergence of memory defects and loss of nerve cells in the hippocampus with advancing age. Similarly, manipulations in early life (neonatal handling, maternal grooming) which keep hormone levels low throughout life, are also associated with the prevention of memory defects with age. Most importantly, recent data show that in ageing normal human populations, those individuals with rising glucocorticoid levels with age subsequently show loss of memory function and shrinkage of the hippocampus (assessed by magnetic resonance imaging). In contrast, individuals whose glucocorticoid levels are low or decline with age, maintain their ability to learn and memorise new facts, and do not show loss of hippocampal size with ageing.

"The ethical implications of such life-long interventions are fraught with problems"

Human therapy?

The two manipulations employed to keep glucocorticoids low, removal of the adrenal glands or 'neonatal handling', are of little relevance to human therapy. Adrenal removal is of course inappropriate for treating large numbers of humans to prevent at best a minority from having memory impairments many years later. Moreover, whilst some data suggest that 'early life programming' of glucocorticoid levels occurs in humans, the precise time in development involved and the form of manipulation required are not known. The ethical implications of such life-long interventions are fraught with problems, even if it were possible to be sure that a particular approach to pregnancy or infant care might be 'better' for the brain 70 years later!

Nevertheless, the neonatal studies have suggested that if we could increase the numbers of glucocorticoid receptors in the hippocampus, the brain would be more sensitive to so-called 'negative feedback' control by glucocorticoids. This would then turn down the hypothalamic-pituitary-adrenal axis and glucocorticoid levels would be kept low. Indeed, very recent data suggest that simple antidepressant drugs can increase glucocorticoid receptors selectively in the hippocampus, perhaps preventing the emergence of memory defects with age. Such treatment with existing and generally well-tolerated drugs might be more appropriate for humans in middle life, raising the possibility of therapies to prevent glucocorticoid-associated ageing of the brain. This is an exciting time and critical work must now address whether such simple and relatively acceptable interventions are effective in ageing human populations.

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