

Dysregulation of Hypothalamic-Pituitary-Adrenal (HPA) Axis in Alzheimer's Disease and use of Non Selective and Selective Glucocorticoid Receptor Modulators to Improve Cognitive function – Review of Literature

Sonia Afshariyamchlou*, Arash Ardabilgazir and Issac Sachmechi

Organized Health Care Education, 8268 164th St Jamaica,
New York 11432, US

*Corresponding author:

Sonia Afshariyamchlou, Organized Health Care Education, 8268 164th St Jamaica, New York 11432, US, Tel: (718) 883-3455; E-mail: soniaafshari.md@gmail.com

Submitted: 15 Aug 2017; Accepted: 22 Aug 2017; Published: 30 Aug 2017

Introduction

Alzheimer's disease (AD) is a relentless neurodegenerative disease affecting more than 36 million people worldwide. Increased evidence suggests stress and its synonymous elevated circulating glucocorticoid levels, due to dysregulation of Hypothalamic-Pituitary-Adrenal (HPA) axis, is an important environmental risk factor for the onset and progression of AD [1]. Here we review recent data on the effect of glucocorticoids on spontaneous activity of HPA axis with particular emphasis on AD, and how modulation of glucocorticoid (GC) levels or GC receptors (GCRs) could potentially mediate disease processes.

Early phase of AD is characterized by hippocampal memory (episodic memory) loss and impaired synaptic plasticity [2]. In a study at IPMC in France on mouse model AD, treatment with GCR antagonist, mifepristone (RU486) reduced cerebral B Amyloid (AB), Tau pathologies and cognitive impairment [3]. Pointing to a potential therapeutic role for interventions to underlying HPA axis and GCRs activity.

Objective

All studies on AD emphasize on heterogeneity of factors involved in disease processes such as: inflammation, glucose metabolism, oxidative stress impairment of mitochondrial function, defect in clearance of defective proteins, mutations in specific proteins, infection, long term response to injury, progressive failure of synaptic transmission, macroscopic cerebral changes in regions involved in learning and memory processes, tau hyper phosphorylation, and accumulation of B Amyloid (AB) [4-6].

Some risk factors like aging and related accumulation of AB as well as mutations in the amyloid precursor protein (APP) are well-established for their neurotoxic effects on cerebral neurons and the development of AD pathology.

The poor correlation between B Amyloidosis and degree of cognitive impairment especially in the early stages of AD, suggests perhaps environmental factors such as stressful life experiences have a role in pathogenesis and progression of AD. In this subject review we try to

shed light on how chronic stress and prolonged exposure to elevated levels of GC impairs the cognitive function and increase vulnerability of particular structures such as hippocampus (HC), which is involved in learning and memory processes, its toxic effects and role of antiglucocorticoid therapy.

Discussion

The brain is constantly exposed to blood concentration of steroids, partly derived from the peripheral pool uptake and partly produced locally (termed "neurosteroids"). It is unclear, however whether these different pools of steroids perform identical or separate functions in the brain [7].

The hippocampus is a brain structure which is crucially involved in episodic memory, the neuroendocrine regulation of stress hormones, and termination of the stress response via HPA axis glucocorticoid-mediated inhibition. Cognitive deficits are associated with a loss of hippocampal neurons, in particular pyramidal cells, due to increased glucocorticoid exposure [8]. Because of the highest number of GC receptors in hippocampus, it is particularly vulnerable to glucocorticoids damaging effects and undergo atrophy under their influence, which is an initial event for the development of AD. Apart from atrophy this down regulate glucocorticoid receptors, which can produce a variety of other functional and structural changes in hippocampus such as 1) Disruption in negative feedback loop, 2) Alteration of dendritic morphology, 3) Impairment of axonal transport which probably is the initial event that leads to formation of paired helical filaments. Also it is reported, stress-level glucocorticoid administration increases Amyloid beta-peptide formation by increasing steady-state levels of amyloid precursor protein (APP) and beta-APP cleaving enzyme. There is now a strong evidence that under stressing condition AB accumulation into soluble oligomers in hippocampus, most probably one of the main triggers of the pathology leading to early synaptic failure and subsequent memory loss, is accelerated. Additionally, glucocorticoids augment tau accumulation, indicating that this hormone also accelerates the development of neurofibrillary tangles. Neuronal survival and function depend mainly on axonal transport. Cortisol also affects the intracellular calcium concentrations by non-genomic mechanisms

which can alter axonal transport. It is also possible that increased glucose utilization, oxidative metabolisms and ATP production by cortisol regulate the function of axonal transport [9].

In the Central Nervous System (CNS) glucocorticoid's neural functions are largely mediated through the interactions with GCRs. Central glucocorticoid receptors are 1) high affinity mineralocorticoid receptor (MR), which has restricted expression and 2) low affinity glucocorticoid receptor (GR), which has ubiquitous expression. Both GR and MR mediate classical genomic and non-genomic glucocorticoid actions by acting as nuclear transcriptional activators and repressors. Abundant expression of GR in the forebrain and increased activity of the HPA axis in the absence of forebrain inhibition, due to damage of forebrain, contributes to the sequelae associated with GR malfunction [8].

Concerning the HPA axis, glucocorticoids (corticosterone, or cortisol in primates) exert their actions primarily on the hippocampus, which is the brain area richest in glucocorticoid receptors. Two different classes of receptors have been described according to their affinity for different glucocorticoids [10]. They appear to operate as a two-level recognition system in the hippocampus. Type I receptors (MR) are occupied at lower glucocorticoid concentrations than type 2 receptors (GR) [4]. This mechanism probably helps the brain to discriminate between the two different modes of glucocorticoid secretion, via, the circadian rhythm and stress-dependent release. In either case, the receptors ensure the shut-off of the circuit, via a negative feedback mechanism.

GR only activated when GC levels rise as during circadian peak and in response to stress. On the other hand MR are abundantly observed in the hippocampus. Thus, GR expression maybe is not as important for GC action in the human hippocampus as previously thought based on rodent data. Interestingly, regarding neurophysiological function, glucocorticoid levels show an inverted U-shaped curve. This has been suggested to be linked to activation of MR and GR receptors, wherein increased hormone levels have adverse effects, through extensive activation of GR. On a long term basis, increased GC exposure may accelerate neuronal damage. It would be of main interest to study the diurnal rhythmicity of the cortisol axis especially diurnal trough might relate possibly to MR function in AD [5].

Excess of GC is known to exert deleterious effect on the structure and function of the central nervous system, especially the hippocampus. The official journal of Japanese psychogeriatric society describes a patient with AD complicated by elderly onset Cushing's syndrome (CS). The patient had rapid progression of AD, probably due to hypercortisolism of CS. The patient had adrenocorticotrophic hormone independent macro nodular adrenal hyperplasia. Surgical correction of hypercortisolism slowed the progression of brain volume loss and cognitive dysfunction [11].

In Alzheimer's disease (AD), cognitive deficits and psychological symptoms are associated with an early deregulation of the hypothalamic-pituitary-adrenal axis. In a recent study done on rats, in an acute model of AD, it was investigated if antiglucocorticoid strategies with nonselective GR antagonist (mifepristone) and selective glucocorticoid receptor (GR) modulators (CORT108297 and CORT113176), that combine antagonistic and agonistic GR properties, could offer an interesting therapeutic approach in the future. It confirmed the expected properties of the nonselective GR

antagonist (mifepristone or RU486) because in addition to restoring basal circulating glucocorticoids levels, mifepristone totally reverses synaptic deficits and hippocampal apoptosis processes. However, mifepristone only partially reverses cognitive deficit, effects of the hippocampal amyloidogenic pathway, and neuroinflammatory processes, suggesting limits in its efficacy. By contrast, selective GR modulators (CORT108297 and CORT113176 at a dose of 20 and 10 mg/kg, respectively,) reverse hippocampal amyloid- β peptide generation, neuroinflammation, and apoptotic processes, restore the hippocampal levels of synaptic markers, re-establish basal plasma levels of glucocorticoids, and improve cognitive function [12].

Conclusion

"According to recent studies there is strong evidence that elevated levels of GC, which is a reflection of high HPA axis activity, is linked to rapid deterioration of cognitive functions in AD, on the other hand hypercortisolism is correlated with hippocampal atrophy and general reduction of brain volume [4]."

Also in normal aging, failure of the adrenal GC regulation results in acceleration of hippocampal damage. In experimental models of neurodegenerative disease, chronic stress and its synonymous glucocorticoid or exogenous glucocorticoid treatment was found to exacerbate both the clinical symptoms and neurodegenerative processes. However recent evidence also suggest that GC-GR has a neuroprotective effect as well. Thus for any possible therapeutic strategy, we need to understand the precise modifications to be made both in HPA axis and in GR and MR activity, to harness their protective actions. Selective GR modulators are particularly attractive and may pave the way to new strategies for AD treatment.

References

1. Yash B Joshi, Jin Chu, Domenico Patino (2012) Stress hormone leads to memory deficits and altered Tau phosphorylation in a model of Alzheimer's disease *JAD* 31:167176.
2. Fabrien Lante, Magda Chafai, Elisabeth Fabienne Raymond, Ana Rita Salgueiro Pereira, Xavier Mouska, et al. (2015) Subchronic glucocorticoid receptor inhibition rescues early episodic memory and synaptic plasticity deficits in a mouse model of Alzheimer's disease. *Neuropsychopharmacology* 40: 17721781.
3. Vikas Dhikav, Kuljeet Singh Anand (2007) Glucocorticoids may initiate Alzheimer's disease: a potential therapeutic role for mifepristone (RU486). *Medical Hypotheses* 68: 1088-1092.
4. Huang C, Lui C, Chang W, Fong TG, Jones RN, et al. (2009) Elevated basal cortisol level predicts lower hippocampal volume and cognitive decline in Alzheimer's disease. *J Clinical Neurosci* 16: 12831286.
5. Elgh E, Lindqvist Astot A, Markku Fagerlund, Sture Eriksson, Tommy Olsson, et al. (2006) Cognitive dysfunction, hippocampal atrophy and glucocorticoid feedback in Alzheimer's disease. *J Biopsych* 59: 155161.
6. Popp J, Wolfsgruber S, Heuser I, Oliver Peters, Michael Hüll, et al. (2015) Cerebrospinal fluid cortisol and clinical disease progression in MCI and dementia of Alzheimer's type. *J Neurobiology of Aging* 36: 601607.
7. Martignoni E, Costa A, Sinforiani E, Liuzzi A, Chiodini P, et al. (1992) The brain as a target for adrenocortical steroids: cognitive implications. *Psychoendocrinology* 17: 343354.
8. Paul S, Jeon W, Bizon J, Han J (2015) Interaction of basal

-
- forebrain cholinergic neurons with the glucocorticoid system in stress regulation and cognitive impairment. *J Front. Aging Neurosci* 7: 43.
9. Guldiken S, Guldiken B (2008) Subclinical cushing's syndrome is a potential cause of metabolic dementia and rapidly progressive Alzheimer type dementia. *J Medical Hypotheses* 71: 703705.
 10. Reul JM, de Kloet ER (1985) Two receptors system for corticosterone in rat brain: microdistribution and differential occupation. *J Endocrinology* 117: 25052511.
 11. Haraguchi, Mizoguchi, Noguchi, Arai, Fukuyama, et al. (2016) A patient with Alzheimer's disease complicated by elderly-onset Cushing's syndrome who had undergone surgical treatment for adrenocorticotrophic hormone-independent macronodular adrenal hyperplasia. *Psychogeriatric* 16: 274-276.
 12. Fanny Pineau, Geoffrey Caneta, Catherine Desrumaux, Hazel Hunt, Nathalie Chevalliera, et al. (2016) *Neurobiology of Aging* 45: 109-122.

Copyright: ©2017 Sonia Afshariyamchlou, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.