Review
ISSN 2413-0516

Chronic Psychosocial Stress Reveals Alzheimer's Disease in a Novel at-risk Rat Model

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(Submitted: 18 December 2022 – Revised version received: 14 January 2023 – Accepted: 25 January 2023 – Published online: 26 February 2023)

Abstract

Extensive individual variations in the time of onset and severity of the sporadic type of Alzheimer's disease (AD), may be due to some patient-related external factors. Stress is increasingly recognized as an external factor in the development of AD. Several labs, including mine, have demonstrated that chronic stress or corticosterone administration aggravates the disease in both transgenic and non-transgenic animal models. We have developed a novel rat model that simulates seemingly normal individuals who are predisposed to develop AD. This review summarizes the findings we have reported on the effect of chronic psychosocial stress in this at-risk model of AD. Behavioral (learning and memory tests), electrophysiological (evoked long-term potentiation) and molecular (protein levels of memory-related signaling molecules a well as AD-related molecules. Our findings suggest that even mild psychosocial stress noticeably transforms this seemingly normal rat model to a full-fledge AD phenotype.

Keywords: Rat AD model, amyloid-beta, learning and memory, signaling molecules

Introduction

Alzheimer's disease (AD) is an insidious gradual decline of intellectual and emotional wellbeing. The disease is characterized by extraneuronal accumulation of high levels of the neurotoxic amyloid-beta (Aβ) peptides, followed later by intracellular accumulation of abnormal tau, a necessary protein for the functioning of intracellular microtubules. Hyperphosphorylation of tau protein can lead to neuronal death and gradual loss of mental abilities.[1,2]

The early symptoms of AD develop slowly and include loss of memory and cognitive skills sometimes with menacing personality changes. The two forms of AD are the early-onset familial type and the sporadic type. The early-onset familial form is rare, representing less than 1% of all cases of AD, and may start as early as age 40, and is due to mutations in the genes for amyloid precursor protein (APP). The second type of AD, the late-onset sporadic, which generally starts after age 60, constitutes the vast majority of AD cases. The sporadic nature of the late-onset disease indicates an environmental link that may hasten the emergence of AD symptoms. In addition to its late onset, the variation in susceptibility to and time of onset of the disease suggests that, aside from possible genetic factors, environmental determinants, including chronic stress, may play a critical role in the severity of sporadic AD.[3–6]

It is commonly believed that the cognitive deficits in AD result from progressive synaptic dysfunction and irreversible neurodegeneration, which are probably initiated by soluble small oligomeric Aβ peptides, in particular the Aβ1-42 form. Progressive malfunction of synaptic transmission occurs during development of AD begins as a localized reduction in synaptic function and gradually progresses to large-scale impairment of neurotransmission in the brain.[7–9]

The earlier amyloid cascade hypothesis has been substantially revised to explain the weak correlation of the severity of dementia with the amount of neuronal loss and extent of the amount of the toxic Aβ in the AD brain. The new idea is that soluble Aβ can cause cognitive impairment in the absence of neurodegeneration.[10] Soluble toxic Aβ can disrupt all forms of synaptic plasticity, including long-term potentiation (LTP), which is widely accepted as the cellular correlate of learning and memory.[11]

Chronic stress is known to intensify the destructive changes seen with various brain disorders including schizophrenia,[12] Cushing's disease (Whitworth et al., 2000),[13] hypothyroidism,[14–16] and AD.[3–5] Reports of hypercorticostroidism in AD patients[17,18] and from animal model studies[19,20] infer that glucocorticoids may contribute to the regulation of APP levels suggesting involvement of the stress hormones in the pathogenesis of AD. In fact, epidemiological studies show that individuals under chronic stress are more prone to get mild cognitive deficits, or even AD, than non-stressed individuals.[21,22] Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis can be a result of exposure to severe and/or prolonged mental stress, which leads to harmful changes in the brain morphology and function.[23,24]

The Hippocampal formation is a brain region particularly vulnerable to the detrimental effects of stress. It is among the first brain areas to succumb to the assault of AD as indicated by substantial impairment of the hippocampus-dependent cognitive capacities. My laboratory has reported that chronic intracerebroventricular infusion of pathogenic doses of Aβ peptides in chronically stressed rats impairs learning and memory and negatively impacts long-term potentiation (LTP) in the hippocampal area CA1.[3,4,25] The combination is more harmful than either chronic stress or Aβ infusion alone.

In this project, we wanted to establish if chronic stress accelerates the emergence of AD symptoms in normal individuals who are at-risk for developing this disease. We have generated a novel rat model meant to represent normal individuals who are vulnerable to develop AD but are not yet showing AD symptoms.

The Symptom-free at-risk AB Rat Model of AD

Exogenous Aβ administration models of AD as well as transgenic models have limitations in that both models do not fully reproduce the complexity of the human AD pathology. Injection of Aβ peptides into the brain may produce some injury at

the site of injection, which could contribute to the inflammatory processes. Administration of Aβ may also cause neurodegeneration, inflammation and microglial activation.[26,27] These unwanted effects of the procedure can be rectified to a significant extent by adjusting the infusion rate, the volume of injection and the recovery time.

The Aβ effect is dose-dependent both *in vitro*[28–31] and *in vivo*.[32–34] This indicates that the neurotoxic effects of Aβ appear only after it achieves a threshold concentration. We have developed a unique at-risk AD rat model by intracerebroventricular (icv) infusion of a sub-pathogenic concentration of Aβ (sub Aβ).

We carried out several various tests with results indicating that unstressed, this model of AD is not significantly different than control rats. This is a new non-transgenic rat AD model that reproduces a human condition where there is vulnerability to AD with no noticeable cognitive impairment. However, when this at-risk AD rat model is generated in rats undergoing chronic stress, these rats show AD symptoms similar to those previously reported in a full-fledged model of AD, where rats received full toxic dose of Aβ.[3] This model represents individuals who appear normal but can develop AD dementia when exposed to stressful conditions.

Animal Groups and Treatments

To analyze the effects of chronic psychosocial stress on our at-risk AD model, Wistar rats were assigned into four experimental groups: control, stress, sub Aβ, and stress/subAβ. The stress and stress/subAβ groups underwent psychosocial stress for 6 weeks. Then, the subAβ and stress/subAβ groups were infused, icv, with sub-pathogenic concentration (160 pmol/day) during the fifth and sixth weeks using 2-week osmotic pumps. This dose was established by constructing a dose-response relationship (Aβ doses-performance in the memory test maze, the RAWM). The control and stress groups were infused with the inactive reverse peptide, Aβ42-1 (160 pmol/day).[35,36]

For chronic stress, an "intruder" form of psychosocial stress was chosen.[37] It was carried out as follows: Rats in the stress groups (2 cages with 6 rats/cage) were kept together undisturbed for one week to allow rats to acclimate and establish social hierarchy. Then chronic stress was initiated by daily random switching of two rats from each cage to other cage for a period of six weeks. We showed that this type of chronic psychosocial stress markedly increased blood corticosterone level[38] and elevated blood pressure.[39]

Behavioral Tests: the Radial Arm Water Maze Task

The radial arm water maze (RAWM: Figure 1A) is a black circular pool (diameter: 1.5 meter) filled with water at room temperature with six V-shaped stainless-steel structures arranged to create six swim paths (arms) radiating from one open central area (see full description in Gerges et al., 2004a).[14] The RAWM is a reliable behavioral test for analyzing hippocampus dependent spatial learning and memory. It can be viewed as a hybrid of the radial arm maze and the Morris water maze (see Figure 1A). The RAWM combines the spatial complexity of the radial arm maze with the motivated fast learning of the Morris water maze but avoids shortcomings in these two mazes.[40–42]

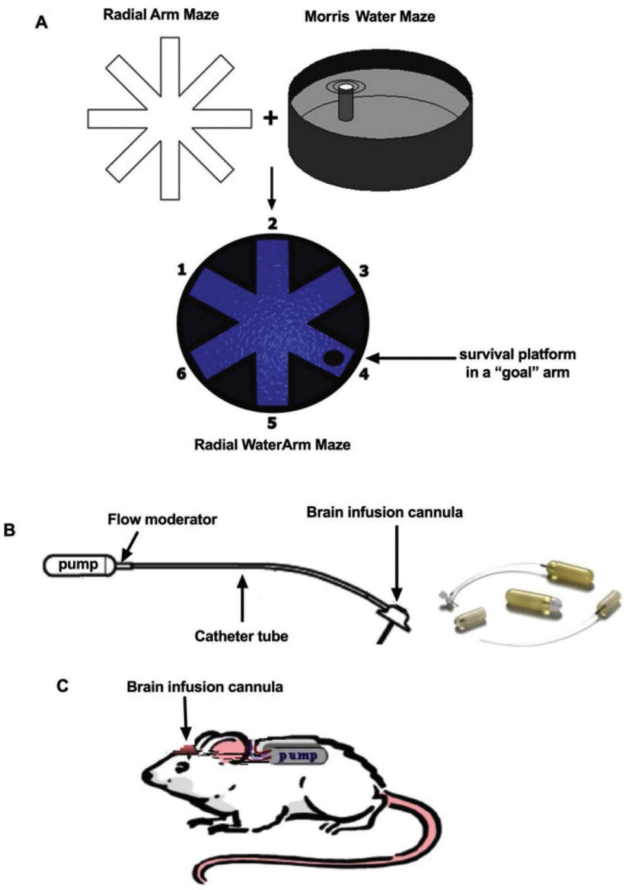

Fig. 1 **The methods: (A) Diagrams of the construction of the radial arm water maze (RAWM) in relation to Morris water maze (MWM) and radial arm maze (RAM). In the RAWM, the light blue regions are the swimming central and arms field. The opaque oval in arm 4 is the submerged platform. (B) The mini-osmotic pump assembly. The stainless-steel short cannula is inserted through a burr hole in the skull into the cerebral ventricle. (C) Positioning of the mini-osmotic pump in the lateral cerebral ventricle of the rat.**

The training protocol for each rat in the RAWM involves a memory acquisition (learning) phase consisting of four one-minute successive learning trials. This is then followed 20 min later by a short-term memory (STM) test, and 24 hr later by a long-term memory (LTM) test. The rat will have to find a platform hidden 1 cm below the water level at the far end of one of the six swim arms. Each time the rat entered an arm other than that containing the hidden platform an error was scored. This procedure was repeated for a minimum of 8 consecutive days.[3–6,35,36]

Learning, Short-term Memory and Long-term Memory

Throughout the initial days of testing, the ability of rats in all 4 groups (control, stress, subAβ and stress/subAβ) to learn the location of the survival platform during the four acquisition phase trials is initially similar as rats learned the location of the hidden platform. However, particularly in the fourth trial, the number of errors committed by the stress/subAβ rat group is significantly increased. This indicates that the learning ability of the stress/subAβ group is markedly impaired as days went by[35] (Figure 2A).

The short-term memory (STM) is tested 20 min after the last learning trial. As expected, stress alone impairs STM in the

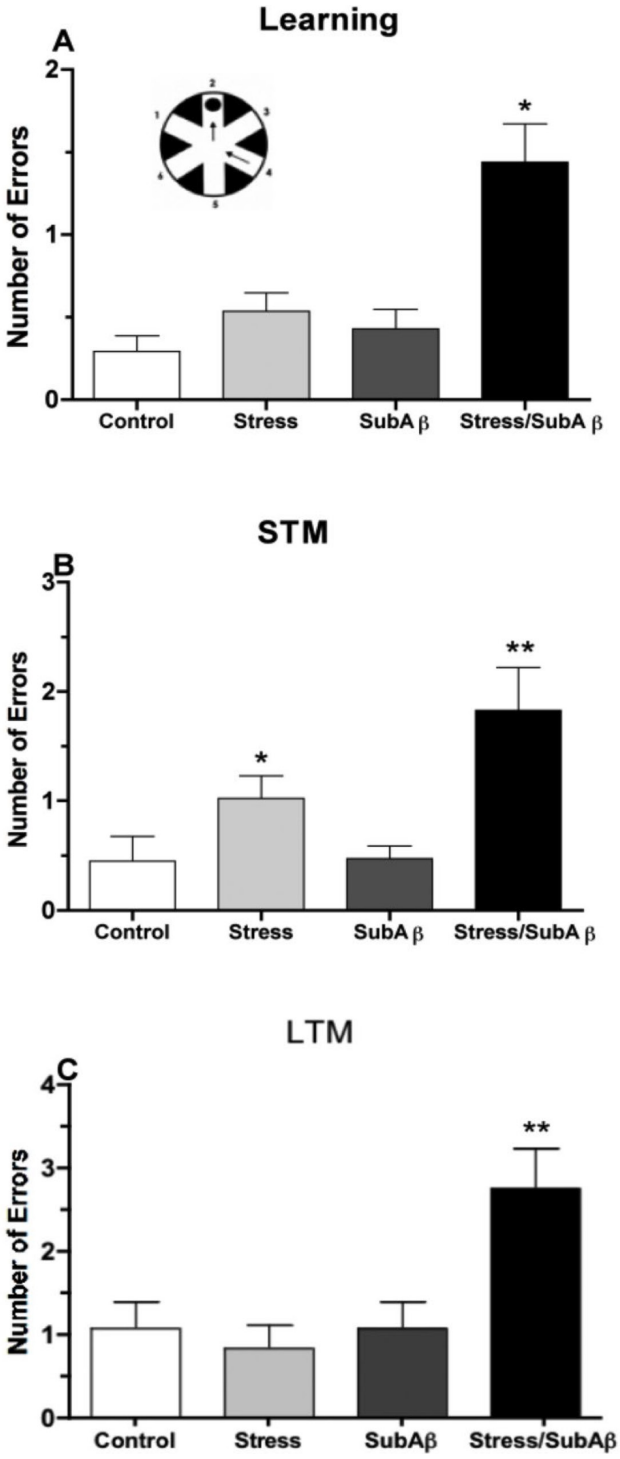

Fig. 2 **The radial arm water maze (inset at panel A) tests show diminished learning and memory in the stress/subAβ rats. (A) The number of errors made by all groups in the last learning (trial number 4. days 6–8 averaged). More errors are committed by the stress/subAβ group than any other group. (B) The short-term memory test (STM, measured 20 min after the last learning trial) is more severely impaired in the stress/subAβ rats than the other three groups. (C) The long-term memory (LTM) test was conducted 24 h after the last learning trial, shows severe impairment in rats of the stress/subAβ group. In all tests, the unstressed subAβ rats are cognitively normal and are not significantly different from control rats. (*= *P* <0.05, **= *P* <0.001, *n* = 12 rats/group; mean ± SEM).**

chronically stressed rat group by making significantly higher number of errors compared to both control and subAβ groups (Figure 2B). Even more interesting; the stress/subAβ group has impaired STM by making significantly more errors than all other groups, including the stress group. These findings are further confirmed by a second test; the days to criterion (DTC), which reveals that the stress/subAβ rats need significantly ($P < 0.05$) more days to reach a criterion than the other three experimental groups. (This criterion is defined as the number of days in which the rat makes no more than one error in three consecutive days).[35]

In the long-term (24 hr) memory test, the stress/subAβ animals have made significantly more errors than the control, stress, and subAβ groups (Figure 2C). Notably, the 6-week chronic psychosocial stress did not affect long-term memory in the stress alone group, confirming our earlier reports.[37,43] In support, the DTC test (not shown) reveals that the stress/subAβ rats need significantly more days to reach the criterion than the other three experimental groups.[35]

Levels of Cognition-related Signaling Molecules

To understand how stress hastens the appearance of AD symptoms in the at-risk (subAβ) rats and to correlate these findings with the results from the learning and memory studies. we examined the underlying molecular mechanism. We used western blot (immunoblot) analysis to measure the levels of principal cognition-related signaling molecules in this preclinical AD model and the effects of chronic psychosocial stress.

Calcium Calmodulin Kinase II (CaMKII)

Stress generally decreases the levels of CaMKII; however, certain forms of stress may upregulate CaMKII expression. For instance, stress caused by postnatal maternal deprivation and pubertal immobilization upregulates CaMKII.[44] The reason for this differential response is not well understood.

The critical role of CaMKII in the memory processes and synaptic plasticity is well studied. Long-term potentiation (LTP), a type of synaptic plasticity, is believed to be the cellular correlate of learning and memory. The accepted molecular cascade of events leading to the formation of the active phosphorylated CaMKII (p-CaMKII) and eventually expression of LTP can be experimentally initiated by high frequency stimulation of the synaptic pathway. It is generally recognized that high frequency stimulation (HFS) initiates presynaptic release of the neurotransmitter glutamate, which activates glutamate receptors on the postsynaptic membrane, causing Ca^{2+} entry through *n*-methyl-D-aspartate (NMDA) glutamate receptor.[45–47] This transient increase of intracellular Ca^{2+} leads to activation of protein kinase C gamma (PKCg), which phosphorylates neurogranin molecule, causing separation of calmodulin from the neurogranin-calmodulin complex.[48,49] The free calmodulin forms a calcium/calmodulin complex, which binds to and activates CaMKII. Activation of CaMKII enables it to self-phosphorylate (autophosphorylation).[50,51] Autophosphorylation makes CaMKII intrinsically active (p-CaMKII), where it activates alpha-amino-3-hydroxy-5-methyl-4-isoxazole (AMPA) glutamate receptors and the synaptic vesicle-specific protein, synapsin, both of which are

important for LTP expression and memory formation.[47,52–54] The activation of these protein molecules by p-CaMKII continues even when intracellular Ca^{2+} concentration returns to normal levels and ends only when it is dephosphorylated by protein phosphatases including calcineurin.[52,55,56] It has been suggested that p-CaMKII may be acting as a molecular switch that changes temporary Ca^{2+} signals into long-term biochemical changes that creates synaptic plasticity leading to memory formation.[57]

Pathogenic doses of Aβ peptides or chronic psychosocial stress significantly reduced the levels of p-CaMKII without changing the levels of total CaMKII.[3] The levels of both p-CaMKII and total CaMKII in the subAβ rats were not significantly different than those in control rats.[35] However, in both the stress/subAβ and stress groups, the p-CaMKII levels were significantly down regulated compared to control and subAβ groups (Figure 3A), with no significant change in the levels of total CaMKII.[35] These findings suggest impairment of the mechanism of CaMKII phosphorylation and/or enhanced dephosphorylation. The finding that the levels of the phosphatase (dephosphorylating) enzyme, calcineurin are markedly increased in the stress/subAβ and stress groups compared to control and subAβ groups (Figure 3C)[35] strongly reinforce the proposition of enhanced dephosphorylation.

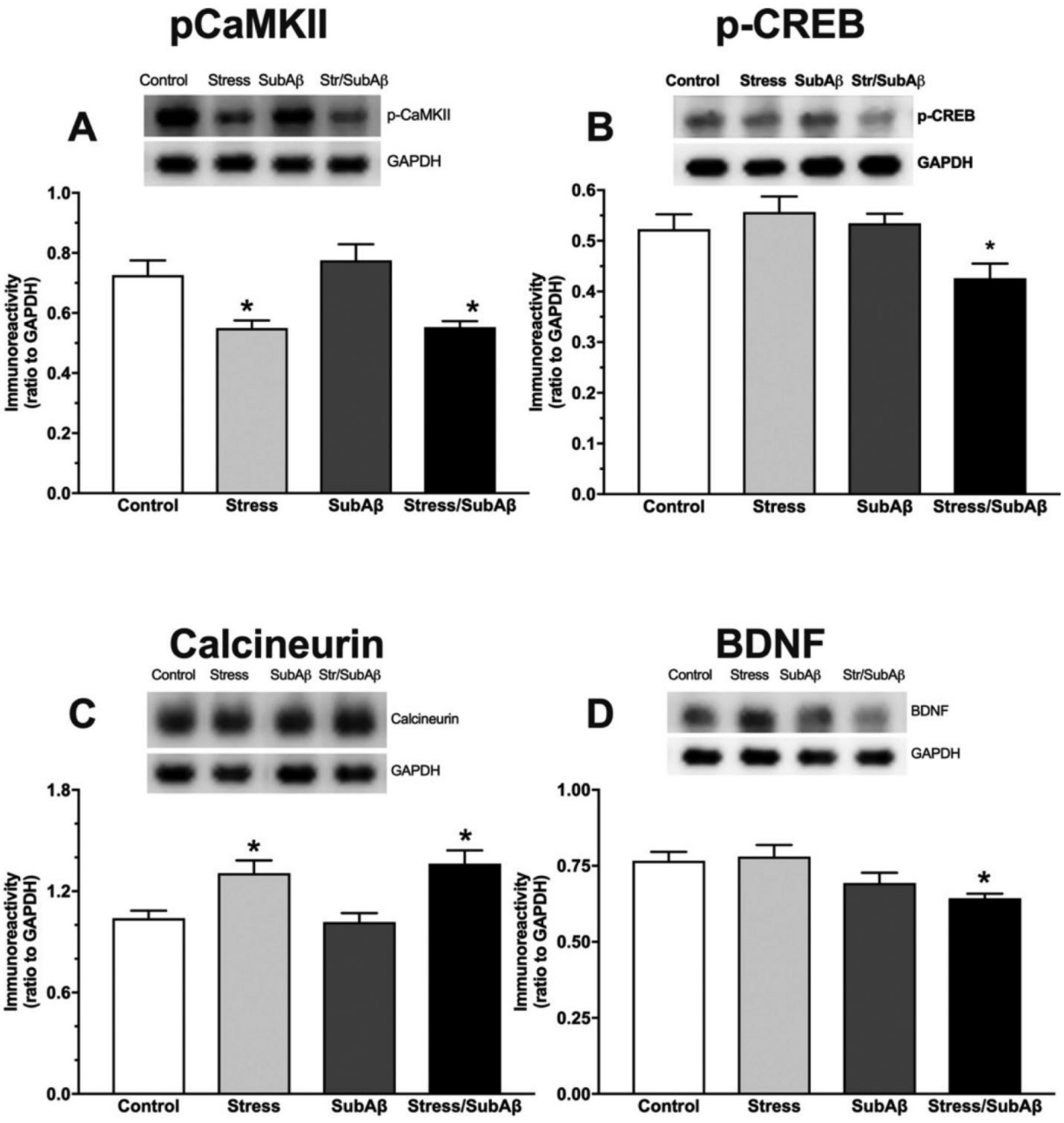

Fig. 3 **The effects of chronic stress and at-risk model on memory-related major signaling molecules in the hippocampal area CA1. (A) Levels of p-CaMKII in stress and stress/subAβ groups are significantly lower (*$P < 0.05$–0.01, $n = 6$–7 rats/group) than in the control and subAβ groups. (B) p-CREB levels are significantly decreased (*$P < 0.05$, $n = 5$–6 rats/group) only in the stress/subAβ group. (C) Shows a significant increase in the levels of calcineurin (*$P < 0.05$–0.01, $n = 7$–8 rats/group) in stress and stress/subAβ groups. (D) There is a significant decrease (*$P < 0.05$, $n = 6$–7 rats/group) in the levels of BDNF only in stress/subAβ group. All results are expressed as mean ± SEM. Insets in all panels are representative western blots. (From Alkadhi, 2023).**

Calcineurin

Phosphorylated signaling molecules, including p-CaMKII, are typically dephosphorylated (inactivated) by protein phosphatases, primarily calcineurin. Calcineurin dephosphorylates inhibitor 1 protein, which regulates protein phosphatase 1 (PP1).[58] This enzyme is efficient dephosphorylator of p-CaMKII.[59] The hippocampus region of the brain contains several phosphatases; of which calcineurin is the principal phosphatase engaged in the regulation of synaptic plasticity. Calcineurin is implicated in the induction and maintenance of long-term depression (LTD),[60] which diminishes postsynaptic activity in hippocampal neurons.[61] Moreover, increased levels of calcineurin in the hippocampus block LTP[62] and diminish hippocampus-dependent memory formation in mice.[63]

Chronic psychosocial stress triggered upregulation of calcineurin in area CA1 of the hippocampus.[3,14,37] Different stressors may produce different effects on the levels of calcineurin. For instance, stress produced by predator exposure has no significant effect on the expression of calcineurin in various regions of rat brain.[64] Remarkably, calcineurin expression in the hippocampus of rats depressed by maternal deprivation, is gender-specific; in that it is decreased in male but not female animals.[65] Astonishingly, in the hippocampal formation, the dentate gyrus (DG) area seems to be resistant to the impact of moderately chronic stress, which produces a significant decrease, rather than an increase, in calcineurin levels. Thus, the DG area seems to have a defense mechanism against chronic stress whereby calcineurin levels are reduced in order to maintain normal P-CaMKII levels. This quality may be responsible for the normal early LTP of the DG area in chronically stressed rats.[66] It is reasonable to assume that this quality is there to preserve neurogenesis, which is a vital function of the DG.

Elevated calcineurin has a negative effect on cognition and appears to be involved in AD pathogenesis.[67,68] Examination of AD brains shows that mRNA of calcineurin is increased in pyramidal neurons of the hippocampus, suggesting that calcineurin has an important role in the pathogenesis of AD.[69] Moreover, treatment of mice (AD model: Tg2576) with the calcineurin inhibitor tacrolimus reverses cognitive impairment.[70] Experiments on cultured cortical neurons showed that disruption of amyloid precursor protein (APP) function was due to a calcineurin-dependent breakdown of another calcium calmodulin kinase, CaMKIV, and its nuclear target Cyclic AMP response element binding (CREB) protein.[71] The disruption of APP results in neurite degeneration, oxidative stress, nuclear condensation and cell death. Furthermore, calcineurin activation in astrocytes is associated with the formation of reactive inflammatory processes related to AD.[72]

In the subAβ rats, calcineurin levels in area CA1 of hippocampus were normal and not significantly different than those in the control group. However, CA1 areas of both the stress and the stress/subAβ groups showed significantly increased levels of calcineurin (Figure 3C). Similar increases in calcineurin levels were seen in the CA1 area of rats treated with a full pathogenic dose of Aβ peptides.[3]

Cyclic AMP Response Element Binding (CREB) Protein

Active CREB signaling pathway performs an important function in mediating the effects of chronic stress on calcium current, LTP and neurogenesis in the DG area.[73] Results from my lab consistently revealed that moderate chronic psychosocial stress in rats did not significantly influence the expression of p-CREB or total-CREB.[5,6,25]

Phosphorylated CREB (pCREB) is essential for long-term memory formation in mammals.[74] The role of CREB in the impairment of memory and synaptic plasticity in AD has been suggested by several studies. For example, nuclear translocation of pCREB is inhibited by Aβ leading to a decreased in the CRE-mediated responses.[75] In addition, CREB phosphorylation is decreased by Aβ through reduction of activation of NMDA glutamate receptor.[76]

The levels of p-CREB and total CREB in brain area CA1 were significantly reduced in the stress/subAβ group but were normal in control, stress and subAβ rat groups (Figure 3B). Infusion of full pathogenic dose of Aβ caused a significant reduction of p-CREB levels in area CA1 of rats.[5,6]

CREB plays an essential role in the production of proteins required for long-term memory and synaptic plasticity in the brain.[77] Therefore, the reduced levels of CREB seen may explain the impaired long-term memory in the stress/subAβ animals. These results further ascertain that chronic psychosocial stress hastens the emergence of AD symptoms in at-risk individuals.

Brain Derived Neurotropic Factor (BDNF)

Brain-derived neurotrophic factor (BDNF) is a member of a family of neurotrophic factors that includes nerve growth factor, neurotrophin-3, and neurotrophin-4/5. These factors activate various isoforms of tropomyosin kinase (Trk) receptors. BDNF exists at high concentration in hippocampal neurons, where its expression is controlled by neural activity. BDNF sustains synaptic plasticity and supports survival of existing and new neurons in the central nervous system. BDNF supports survival of neurons in the cortex,[78] hippocampus[79] and basal forebrain.[80] It is released after tetanic stimulation to modulate the induction and maintenance phases of LTP in the hippocampus.[36,81,82] The role of BDNF in memory processes is recognized when expression of its mRNA is correlated with performance in various cognition tests.[83,84] The essential role of BDNF in synaptic plasticity and memory, supports the assumption that its loss may add to memory dysfunctions associated with neurodegenerative diseases including AD. Additionally, it has been reported that exposure to various stressors both acute[85] and chronic can significantly down regulate both BDNF mRNA expression and protein levels in the hippocampus. In fact, autopsied AD brains show marked reduction of BDNF mRNA and protein in the hippocampus and temporal cortex of.[86] However, there are conflicting reports concerning the levels of BDNF in the brains of animal models of AD. The reason for this discrepancy is unclear; it may be due to an assortment of factors including the type of AD model used, the dose level of Aβ administered, different phases of the disease at which the levels of BDNF was determined etc.

We showed a significant decrease in BDNF levels in the brains of rats of the stress/subAβ group compared to its levels in stress and subAβ animal groups, which are not significantly changed.[6,87] Similar findings have been reported on the effect of sub-lethal dose of Aβ in cultured cortical neurons.[88] My lab reported significantly higher levels of BDNF in rats infused with a full pathogenic dose of Aβ.[5] This may sound inconsistent but can be interpreted as an attempt by the brain cells to achieve repair at this stage of the disease.

Alzheimer's Disease-Relate Proteins

The source of Aβ is a transmembrane protein called amyloid precursor protein (APP). The domain of APP is partly embedded in the plasma membrane where it can be cleaved. Cleaving and processing of APP can occur through two major pathways: a non-amyloidogenic pathway, which generates non-toxic Aβ peptides, and an amyloidogenic pathway that produces the pathogenic peptides.[89] The cleaving of APP can occur through cutting by three enzymes: α, β, and γ secretases. The major non-amyloidogenic pathway is started by α-secretase slicing of APP within the Aβ domain, thereby preventing the creation of pathogenic Aβ forming a harmless large soluble APP fragment (soluble alpha-amyloid precursor protein; α-sAPP).[89] In the amyloidogenic pathway, the making of Aβ peptides begins with the proteolytic cleaving of APP just above the Aβ domain by β-secretase discharging the soluble beta-amyloid precursor protein (β-sAPP) fragment and generating the C-terminal fragment 99 (C99). The β-sAPP is then cleaved by γ-secretase to release the pathogenic Aβ peptides.[89] The majority of β-secretase activity originates from a membrane aspartyl protease called β-site APP cleaving enzyme 1 (BACE1), which serves as the rate limiting step in the production of pathogenic peptides.

We studied the levels of APP in area CA1 of the four experimental groups using immunoblot analysis. No significant change in the APP levels is seen in the stress, subAβ or stress/subAβ compared with those of the control group (Figure 4A). The levels of BACE in area CA1 are normal in stress or subAβ rats, however, chronic stress significantly increases the levels of BACE in stress/subAβ group compared with control, stress, and subAβ rats (Figure 4B). The elevated levels of BACE in stress/subAβ rats suggests that the processing of APP though the pathogenic pathway is enhanced in these animals. Consistent with these finding, we also have reported that full pathogenic Aβ dose (300 pmol/day) caused a significant elevation of BACE in area CA1.[4]

Possible Mechanisms of the Negative Effects of Stress

Abnormal levels of Aβ peptides in the brain interrupt phosphorylation of CaMKII and interfere with LTP induction.[4,90,91] Previously, we have shown that chronic stress decreases the levels of p-CaMKII and reduces the magnitude of LTP in hippocampal area CA1.[3,14] As mentioned earlier, CaMKII has an essential role in the development of learning and memory. It is possible that the stress-induced disruption of the CaMKII-dependent protein phosphorylation may enhance the loss of p-CaMKII already caused by Aβ, whereby contributing to the mechanism by which chronic stress impairs memory in this model of AD.

High levels of the stress hormones, corticosteroids, during stressful conditions activates type-II glucocorticoid receptors boosting Ca2+ influx, which results in inhibition of CA1 pyramidal neuronal excitability.[92,93] Earlier reports have suggested that Aβ peptides disrupt intracellular Ca^{2+} signaling[94–96] and inhibit Ca^{2+}-dependent post-translational protein phosphorylation. Additionally, acute application of Aβ in the dentate gyrus during repetitive stimulation causes inhibition of LTP together with a reduction in p-CaMKII levels.[91] Therefore, it is understandable that stress worsens Ca^{2+} -dependent signaling processes in Aβ rats.

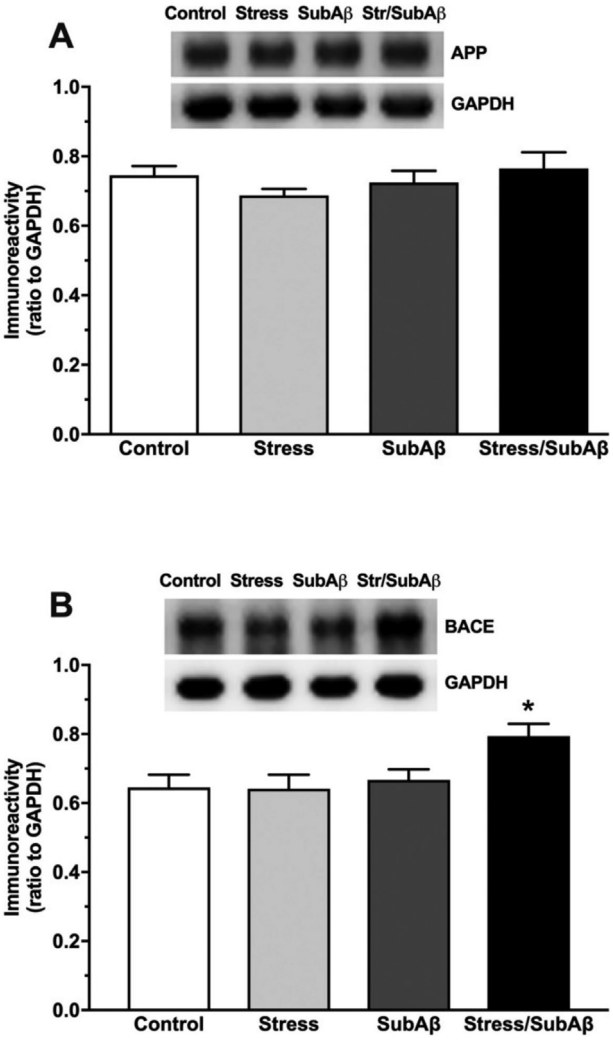

Fig. 4 **Levels of AD-related proteins. (A) No significant changes in the levels of amyloid precursor protein (APP) of area CA1 were observed among the four experimental groups. (B) Chronic stressing of subAβ group (stress/ subAβ) significantly increased the basal level of BACE in these rats. Results are expressed as mean ± SEM. (*) Significant difference from other groups ($P < 0.05$, $n =$ 6–7 rats/group). Insets in both panels are representative blots. (From Tran et al. 2011).**

As an attempt by the brain to reduce injury, the levels of neurotrophic factors, including BDNF, are elevated in specific brain areas in reaction to various types of disorders, including traumatic brain injury, seizure, ischemia and neurotoxins.[97,98] BDNF plays a major role in neuronal health and survival.[99] A protective mechanism may be activated in the early stages of AD to counter the Aβ-induced neurotoxicity. This is suggested by previous reports that show an enhanced mRNA of BDNF in the hippocampus[100] as well as increased protein levels of BDNF in the forebrain in APPsw mice model of AD[101] and in area CA1 in the full dose Aβ-treated rats.[4] In contrast, we have shown that chronic stress significantly decreases BDNF levels in area CA1 of the hippocampus.[37] Therefore, by reducing the availability of BDNF, stress hinders the repair process and consequently boosts the effect of Aβ.

At the subcellular level, mental stress and AD seem to interfere with mitochondrial function by a similar mechanism. The mitochondrial enzyme that binds to Aβ peptide directly is 17β-hydroxysteroid dehydrogenase type 10 (17β-HSD) or the

Aβ-binding alcohol dehydrogenase (ABAD). It has been shown that mental stress impaired mitochondrial function and increased ABAD expression in the brain therefore, it is possible that increasing ABAD by chronic stress brings mitochondrial dysfunction to a critical threshold level required to show clear AD phenotype.

Stress modifies the processing of various proteins involved in the expression of AD. Glucocorticoids and stress exposure are shown to increase the concentrations of APP and BACE proteins, signifying that stress may be forcing the processing of APP toward the pathogenic pathway. Such effect explains the enhanced levels of pathogenic Aβ protein[3,4,102] and the increased plaque formation[85] that have been reported with stress.

In summary, chronic stress has a profound effect on the course of development of AD. In several studies with various experimental approaches, my lab has shown the negative impact of chronic psychosocial stress on the development of dementia in a novel rat model that simulates seemingly normal individuals susceptible to developing AD (at-risk for AD). The findings of these studies have shown that exposure to chronic stress in these individuals accelerates the progress of AD symptoms.

Acknowledgments

The author appreciates the technical support for this review from the Department of PPS.

Conflicts of Interest Disclosure

The author declares no actual or potential conflict of interest related to this review.

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