Chronic Stress Accelerates and Intensifies Aβ-induced Alzheimer's-disease-like Pathogenesis in Rat Models

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Abstract

Apart from genetic factors, environmental factors such as stress may also play a critical role in the manifestation of Alzheimer's disease (AD). We studied the impact of chronic psychosocial stress in two amyloid-beta (Aβ) rat models of AD by three approaches: learning and memory tests in the radial arm water maze, electrophysiological recordings of long-term potentiation (LTP) in anesthetized rats, and immunoblot analysis of synaptic plasticity- and cognition-related signaling molecules. The first Aβ rat model, representing established AD, was induced by continuous intracerebroventricular (ICV) infusion of a pathogenic dose of Aβ peptides via a 14-day osmotic pump. In this AD model, chronic stress intensified cognitive deficits, produced more depression of LTP, and accentuated the reduction of signaling molecule levels compared with the established model alone. The second model represents subjects that are clinically normal but are at risk for AD, and was induced by ICV infusion of a sub-threshold (sub-Aβ) dose of Aβ peptides. Chronic psychosocial stress was induced using a rat intruder model. Various tests showed that sub-Aβ rats were not significantly different from control rats. However, chronically stressed sub-Aβ rats showed more significant impairment of cognitive functions and early-phase LTP than that caused by stress alone. Molecular analysis revealed marked disturbances in the levels of essential signaling molecules in the stressed AD at-risk rats. These findings suggest that chronic stress may profoundly accelerate and intensify the impairment of cognition and synaptic plasticity in individuals at risk for AD and those with established AD, respectively. Possible mechanisms for the effect of chronic stress are discussed.

Keywords

Rat Alzheimer's disease model, amyloid-beta, learning and memory, signaling molecules, synaptic plasticity

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by extracellular deposition of pathogenic amyloid-beta (Aβ) peptides, intracellular aggregation of hyperphosphorylated tau protein, and neuronal death.[1,2] Molecular studies have shown that missense mutations in genes for amyloid precursor protein (APP), presenilin 1 (PS1), or presenilin 2 (PS2) account for the majority of familial AD cases.[3,4] However, early-onset familial AD represents fewer than 5% of AD cases, while sporadic, late-onset AD is evident in over 95% of cases.[3,4] The sporadic nature of AD suggests an environmental link that may trigger AD pathogenesis. In addition to its late onset, the variation in susceptibility to and time of onset of the disease suggests that, aside from genetic factors, environmental determinants such as chronic stress may also play a critical role in the etiology of sporadic AD. Additionally, during AD a progressive failure of synaptic transmission occurs; it begins as a localized decrease in synaptic function and over time progresses to global impairment of neurotransmission in the brain.[5–7]

Chronic stress is considered a negative modulator of the learning and memory process.[8–12] Stress-induced intensification of cognitive impairment has been reported with various disorders including schizophrenia,[13] Cushing's disease,[14] hypothyroidism,[15] and AD.[16,17] Clinical studies have shown elevated plasma cortisol levels in individuals with dementia and in AD patients.[18–21] Accordingly, it has been postulated that stress may be associated with this disease.[22–24] This is further supported by the epidemiological findings that individuals prone to experiencing psychological distress are more likely to develop mild cognitive impairment, or even AD, than non-stressed individuals.[25,26] Clinical reports of hypercortism in AD patients[18,27] and animal studies[28,29] have shown that glucocorticoids participate in the regulation of APP levels, suggesting involvement of glucocorticoids in the pathogenesis of AD.

Exposure to stress activates the hypothalamic–pituitary–adrenal (HPA) axis, resulting in increased release of glucocorticoids into the bloodstream.[30–32] The high level of glucocorticoids seen under stressful conditions is enough to activate type II glucocorticoid receptors, with negative consequences for hippocampal function.[33,34] Thus, chronic stress can have a deleterious effect on hippocampal structure and function[35] because of the abundance of glucocorticoid receptors in the hippocampus and its involvement in cognition.

Alzheimer's Disease Rodent Models

Although much progress has been made in AD research, the lack of an animal model that reproduces the complex spectrum of pathologies and cognitive symptoms of AD has hindered effective therapeutic development. Several of the neuropathological features of AD have been recapitulated by the introduction of APP, PS1, and PS2 transgenes into mice.[36–41] The majority of transgenic animals exhibit cognitive deficits, amyloid peptide accumulation, and synaptic dysfunction without showing neurofibrillary tangle formation, overt neuronal death, or microglial activation.[42–45] The creation of double- or triple-transgenic mice has increased the phenotypic similarities between animals and humans.[46,47] However, several limitations of transgenic animal models of AD have been identified. First, the cerebrospinal fluid (CSF) of the brains of AD mice contains a constant high concentration of various Aβ peptide species, thereby complicating attempts to study the molecular bases of synaptic dysfunction; and second, the lack of neuronal death suggests that compensatory factors may be triggered by the introduction of transgenes into these mice.[48]

As a complementary alternative to transgenic animal models, non-transgenic models of AD are valuable tools for studying the specific pathogenesis induced by Aβ. Similar to transgenic models, exogenous Aβ administration does not reproduce the full complexity of human pathology. However, studies involving exogenous administration of Aβ have reported neurodegeneration and microglial activation, proximal to Aβ deposits.[49,50] The exogenous Aβ administration model of AD has its own limitations as well. For example, injection/infusion of Aβ peptides is an invasive procedure, particularly when infusion is accomplished via osmotic pump. It introduces inevitable injury at the site of injection/infusion, which possibly contributes to the induction of inflammatory processes. However, these limitations can be overcome to a significant degree by adjusting the infusion rate, the vehicle, the volume of injection, and the recovery time before examination of the animal to minimize the confounding effect of the procedure involved in administering Aβ.

During normal cellular metabolism, neurons secrete low levels of soluble Aβ peptides into the CSF and plasma.[51,52] It has been suggested that the extent to which and the rate at which the pool of soluble Aβ oligomers forms insoluble amyloid fibrils are dependent on the rates of Aβ catabolism and clearance, which determine the amount of Aβ deposition and aggregation into amyloid plaques.[52–55] We recently developed a novel AD at-risk model by intracerebroventricular (ICV) infusion of a non-pathogenic concentration of $A\beta_{1–42}$ for 14 days. Our at-risk rat model of AD is the first non-transgenic rat model that imitates a condition in which there is a heightened susceptibility to AD without any observable cognitive deficits.

Chronic Stress Accelerates and Intensifies Cognitive Deficits

A reliable and sensitive behavioral test for analyzing hippocampus-dependent learning and memory is the radial arm water maze (RAWM). It is a hybrid of the radial arm maze and the Morris water maze that combines the variable spatial complexity of the radial arm maze with the rapid motivated learning of the Morris water maze while minimizing their disadvantages.[56–59]

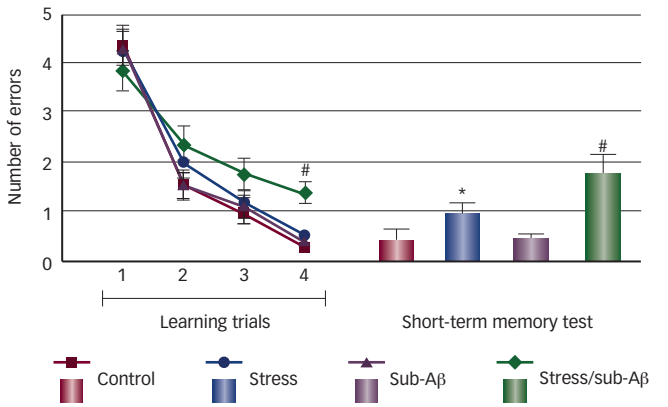
Four experimental groups were used in the study: control, stress, Aβ-treated, and stress/Aβ. The stress and stress/Aβ groups were subjected to stress for six weeks. In addition, the Aβ and Aβ/stress groups were infused with a mixture of $A\beta_{1–40}$ and $A\beta_{1–42}$ (300pmol/day) during the fifth and sixth week. The control and stress groups were infused with $A\beta_{42–1}$, an inactive reverse peptide. The RAWM training protocol consisted of a learning phase of four one-minute consecutive learning trials and a short-term memory test conducted 20 minutes after the last learning trial. The animals had to locate a black platform submerged 1cm below the water level near the end of one of the six swim arms, designated as the 'goal arm.' A correct selection occurred when the rat swam directly to the goal arm, while error was scored each time the rat entered into an arm other than the goal arm. This procedure was conducted for a minimum of eight consecutive days or until the rat reached the days to criterion (DTC). The DTC is defined as the number of days in which the rat commits a maximum of one error in three consecutive days in the fourth learning trial and short-term memory test.[16,17,60]

On days six to eight of testing in the RAWM, the stress/Aβ rat group's ability to learn was significantly impaired compared with all other groups, including the Aβ group. For example, in trial four, stress/Aβ rats made significantly more errors in locating the hidden platform than the other rat groups, including Aβ rats. Furthermore, the Aβ group made significantly more errors than the control and stress rats.[16,17]

Both stress and Aβ groups revealed impairment of short-term memory compared with the control group. However, the stress/Aβ group showed significantly more impairment of short-term memory than all other groups. These results were further confirmed by DTC values. In the learning phase, the stress/Aβ rats required approximately twice the number of days as did the control and stress groups to reach the criterion for learning. Additionally, the Aβ group required significantly more days to reach the criterion than control and stress groups.[16] By contrast, DTC values were not significantly different between control and stress animal groups,[16] indicating that stress alone did not impair learning, which confirmed our published findings.[12] Thus, stress severely exacerbated learning deficits in cognitively impaired animals while having no effect on learning in normal animals. The short-term memory DTC values showed that chronic stress severely exacerbated Aβ-induced short-term memory deficits. This was indicated by nearly twice the number of days required by the stress/Aβ group compared with the stress and Aβ groups.[16]

In our novel at-risk model, four groups were designated as control, stress, subAβ, and stress/subAβ. The results with the at-risk model showed that although the learning ability of rats of the sub-Aβ group (infused with 160pmol/day) was not different from that of the control group, that of the stress/sub-Aβ rats was markedly impaired compared with the other three experimental groups.[60] On days six to eight (see *Figure 1*), the stress/sub-Aβ rats continued to commit significantly more errors in the short-term memory test than all other groups, including the stress group, which itself committed more errors than the control and subAβ groups. In addition, short-term memory was significantly more impaired in the stress/sub-Aβ groups than in the stress group (see *Figure 1*).[60] These findings were further confirmed by the DTC of short-term memory. The stress/sub-Aβ rats required significantly ($p<0.05$) more days to reach the criterion than the other

Figure 1: Impaired Radial Arm Water Maze Performance in Stress/Sub-Aβ Rats



Trials one to four represent the learning phase. The short-term memory test was conducted 20 minutes after the last learning trial. On days six to eight, as indicated by trial four, the stress/sub-Aβ group did not learn the location of the hidden platform at the same rate as the other three groups. During these days, short-term memory was significantly more severely impaired in the stress/sub-Aβ rats than in the other three groups. Note that sub-Aβ rats were cognitively normal, where neither learning nor short-term memory was significantly different from that of control rats.
**Significant difference from control and sub-Aβ groups; #Significant difference from control, stress, and sub-Aβ groups (p<0.05, n=12 rats/group).*
Source: Modified from Tran et al., 2010.[60]

three experimental groups.[60] As expected,[11] the stress group also required significantly more days to reach the DTC than the control and sub-Aβ groups.

Chronic Stress Reveals and Exacerbates Impairment of Synaptic Plasticity

To link cognitive deficits with possible changes in the cellular correlates of memory, we evaluated synaptic plasticity in area CA1 of the hippocampus. We recorded population spikes (pSpike) from area CA1 of anesthetized rats and measured the slope of field excitatory synaptic potential (fEPSP: a measure of synaptic strength) and spike amplitude (a measure of the number of neurons firing action potentials).[61] In these electrophysiological experiments, we first assessed basal synaptic function by applying a range of stimulus intensities to generate input–output (I/O) curves in control, stress, Aβ, and stress/Aβ group animals. The I/O curves of the Aβ and stress/Aβ groups showed a significant rightward shift compared with those of the control and stress groups, indicating impaired basal synaptic transmission in these animals.[16]

Early-phase long-term potentiation (LTP) is believed to be a cellular correlate of short-term memory.[62] We induced LTP by high-frequency stimulation (HFS) in the four groups of rats. Stimulation in control rats induced a robust LTP that lasted at least one hour after HFS. However, in stress/Aβ animals, immediately after HFS, LTP magnitude started to decay such that at 60 minutes post-HFS it completely disappeared down to baseline level. In Aβ and stress/Aβ rats, the pSpike LTP magnitude was significantly lower than that observed in stress rats at all points tested.[16]

In the at-risk model, HFS induced robust LTP in the control and sub-Aβ animals. However, in both the stress and stress/sub-Aβ groups, although the magnitude of LTP was significantly higher than baseline values, it was markedly lower ($p<0.05$) than that of the control and sub-Aβ groups at all time-points after application of HFS. Furthermore, at all time-points, LTP in stress/sub-Aβ animals was significantly lower ($p<0.05$) than that of the stress animals at 60 minutes after HFS.[60]

Chronic Psychosocial Stress Disrupts Levels of Signaling Molecules Essential for Memory and Early-phase Long-term Potentiation

Calcium calmodulin kinase II (CaMKII) plays a critically important role in memory and LTP processes.[41,44,45] Under normal conditions, induction of LTP by HFS leads to a persistent increase in the levels and activity of phosphorylated (p)-CaMKII and calcineurin in hippocampal slices[62,63] and anesthetized animal hippocampi.[16,57–59] Activation of N-methyl-D-aspartate receptor (NMDAR) causes a transient increase in intracellular calcium concentrations, leading to autophosphorylation of CaMKII.[64] The rapid autophosphorylation of CaMKII results in a constitutively active CaMKII[65] that phosphorylates and activates β-amino-3-hydroxy-5-methyl-4-isoxazole (AMPA) receptors and synapsin, which are important for LTP expression.[66,67] It is proposed that activation of CaMKII serves as a molecular switch that converts transient Ca^{2+} signals into long-lasting biochemical changes that underlie synaptic plasticity.[68]

To further elucidate the potential mechanism by which stress exacerbated Aβ-induced impairment of synaptic plasticity, we evaluated the effect of chronic stress on CaMKII phosphorylation one hour after induction of LTP by HFS. As expected, immunoblot analyses revealed marked increases in p-CaMKII levels in the stimulated control compared with the unstimulated control group.[69,70] By contrast, HFS-induced CaMKII phosphorylation was significantly inhibited in stimulated stress, stimulated Aβ, and stimulated stress/Aβ groups compared with stimulated control animals.[16] p-CaMKII is normally dephosphorylated by a protein phosphatase, principally calcineurin, which is a negative modulator of cognitive memory and seems to be involved in AD pathogenesis. For example, inhibiting calcineurin with tacrolimus (FK506) reversed cognitive impairment in Tg2576 mice.[71] We found that the basal levels of calcineurin were increased significantly in the stress, Aβ, and stress/Aβ groups compared with those of the control group.[16] After induction of LTP by HFS, the levels of calcineurin in area CA1 were significantly ($p<0.05$) increased in all groups compared with the stimulated control.

In the at-risk model, one hour after the induction of LTP by HFS in area CA1 of the hippocampus, the levels of p-CaMKII in area CA1 were markedly increased in the stimulated control and stimulated sub-Aβ groups, but not in the stimulated stress and stimulated sub-Aβ/stress groups.[60] The levels of total CaMKII were significantly increased to similar levels in all stimulated groups after the induction of LTP. The levels of calcineurin were also significantly increased in all stimulated groups after the induction of LTP in the CA1 area of the hippocampus.[60]

We have shown previously that chronic stress decreases basal levels of phosphorylated (p)-CaMKII in the CA1 region of anesthetized rats, and subsequently reduces the magnitude of HFS-induced LTP.[16,72] Furthermore, the presence of abnormal levels of Aβ peptides has been shown to disrupt phosphorylation of CaMKII and interfere with LTP induction in both *in vivo* and *in vitro* studies.[16,73,74] Based on findings from our two models, we propose that the mechanism by which chronic

stress impairs memory and LTP in these models of AD may involve decreasing CaMKII-dependent protein phosphorylation.

Possible Mechanisms of the Effects of Stress

In general, activation of mineralcorticoid (type I) receptor by low levels of corticosteroids produces low calcium influx, which has an excitatory effect on hippocampal CA1 pyramidal cells, whereas activation of glucocorticoid (type II) receptor by high levels of corticosteroids during stressful conditions enhances calcium influx and inhibits CA1 pyramidal cell excitability.[34,75] Given the stress-induced glucocorticoid effects on Ca^{2+} dynamics, it is not surprising that stress worsens Ca^{2+}-dependent signaling processes in Aβ rats. This finding is in line with previous reports that Aβ perturbs intracellular Ca^{2+} signaling[76–78] and inhibits Ca^{2+}-dependent post-translational protein phosphorylation.[79] For example, studies by Zhao et al.[73] using acute application of $A\beta_{1-42}$ during HFS showed inhibition of LTP in the dentate gyrus, with corresponding reductions in p-CaMKII levels.

Brain-derived neurotrophic factor (BDNF) plays a major role in neuronal survival.[80,81] The levels of neurotrophic factors, including BDNF, are increased in specific brain regions in response to various types of insults, including ischemia, seizure, traumatic brain injury, and neurotoxins.[82,83] Earlier reports show an increase in BDNF messenger RNA (mRNA) in the hippocampus[84] and increases in protein levels of BDNF in the forebrains of APPsw mice[85] and area CA1 in Aβ-treated rats,[17] which suggests that in early AD a compensatory mechanism is activated to protect neurons from Aβ-induced neurotoxicity. By contrast, chronic stress has been reported to significantly decrease BDNF levels in area CA1 of the hippocampus.[86] Therefore, by limiting the availability of BDNF, stress interferes with the repair process, with the consequence of exacerbating the effect of Aβ.

Interestingly, recent reports have shown that the expression of nerve cell adhesion molecule (NCAM) is increased in the brains of AD patients, indicating neurogenesis.[87] This could be an attempt by the brain to repair or replace neurons lost to the disease. In contrast to AD, chronic stress is known to cause a severe reduction in the levels of NCAM.[88,89] We speculate that the neurotoxic effect of Aβ in the brain might be countered through repair, as suggested by the reported increased levels of NCAM. However, in the presence of chronic stress the ability of NCAM to repair is severely limited by the stress-induced reduction in the concentration of these protein molecules.

Another possibility is that stress may alter the processing and production of various AD-related proteins. It has been shown that exposure to stress or glucocorticoids increases the levels of APP, C99, and beta-site APP-cleaving enzyme (BACE), thus indicating that stress drives the processing of APP toward the amyloidogenic pathway, which may account for the increased levels of Aβ[16,17,90,91] and the increased amount of plaque formation[92] that are also observed with stress.

In summary, the presence of chronic stress accentuates the severity and hastens the appearance of cognition and synaptic plasticity deficits in established AD-model and AD at-risk rats, respectively. This impairment is likely associated with a number of inter-related disturbances of a number of signaling molecules including failure of p-CaMKII to increase after the induction of LTP. The results of these studies suggest that, in addition to the onslaught of Aβ-associated cognitive insults wrought on the AD brain, the coincidence of chronic stress further compromises mental capacities in AD patients and accelerates the emergence of AD in susceptible individuals. ■

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