Chronic Stress and Alzheimer's Disease-Like Pathogenesis in a Rat Model: Prevention by Nicotine

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Abstract: Environmental factors including chronic stress may play a critical role in the manifestation of Alzheimer's disease (AD).This review summarizes our studies of the aggravation of the impaired cognitive ability and its cellular and molecular correlates by chronic psychosocial stress and prevention by nicotine in an Aβ rat model of AD. We utilized three approaches: learning and memory tests in the radial arm water maze, electrophysiological recordings of the cellular correlates of memory, long-term potentiation (LTP) and long-term depression (LTD), in anesthetized rats, and immunoblot analysis of synaptic plasticity- and cognition-related signaling molecules. The Aβ rat model, representing the sporadic form of established AD, was induced by continuous i.c.v. infusion of a pathogenic dose of Aβ peptides *via* a 14-day osmotic pump. In this AD model, chronic stress intensified cognitive deficits, accentuated the disruption of signaling molecules levels and produced greater depression of LTP than what was seen with Aβ infusion alone. Chronic treatment with nicotine was highly efficient in preventing the effects of Aβ infusion and the exacerbating impact of chronic stress. Possible mechanisms for the effect of chronic stress are discussed.

1. INTRODUCTION

Alzheimer's disease (AD) is an irreversible, progressive neurodegenerative brain disorder characterized by extracellular accumulation of pathogenic amyloid-beta (Aβ) peptides, intracellular aggregation of hyperphosphorylated tau protein, and neuronal death [1, 2]. The early symptom of the disease is a slow and insidious destruction of memory and cognitive skills. 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 [3-5]. However the early-onset familial AD represents less than 5% of AD cases, while the sporadic, late-onset AD is evident in the vast majority of the cases [4, 5]. Because of the poor correlation of the severity of dementia with the extent of neuronal loss and degree of fibrillar Aβ load in the AD brain, the original amyloid cascade hypothesis has been substantially revised. It is now thought that certain oligomeric forms of soluble Aβ can cause cognitive impairment in animals in the absence of neurodegeneration [6]. Additionally, synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD), the cellular correlates of learning and memory, are highly vulnerable to disruption by soluble Aβ species [7].

The sporadic nature of this disorder 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 severity of sporadic form of 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 [4, 7, 8].

Chronic stress is a homeostatic challenge with physical and psychological ramifications and a particularly negative effect on the learning and memory process [9-14]. It is known that stress aggravates cognitive impairment in various disorders including schizophrenia [15], Cushing's disease [16], hypothyroidism [17], and AD [18-21]. Based on clinical reports of elevated plasma cortisol levels in individuals with dementia and in AD patients [22-25], it has been postulated that stress may be associated with this disease [26-28]. Further support of this hypothesis comes from epidemiological findings that stressed individuals are more likely to develop mild cognitive impairment, or even AD, than non-stressed individuals [29, 30]. Clinical reports of hypercortism in AD patients [25, 31] and animal studies [32, 33] have shown that glucocorticoids participate in the regulation of APP levels suggesting involvement of these hormones in the pathogenesis of AD. Stress activates the hypothalamic-pituitary-adrenal (HPA) axis resulting in glucocorticoids blood levels high enough to activate type-II glucocorticoid receptors with negative consequences for hippocampal function [34-36]. Because of the abundance of glucocorticoid receptors in the hippocampus and its involvement in cognition, chronic stress can have deleterious effects on the hippocampal structure and function [37].

Most epidemiological studies have reported a highly significant negative correlation between cigarette smoking and AD [38-40, 42 but see 42, 43]. Laboratory and clinical

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studies have shown that nicotine improves cognitive function in AD patients and attenuates Aβ-induced amnesia in rodents [19, 40, 44, 45].The finding that chronic nicotine treatment prevents stress-induced down regulation of central nicotinic acetylcholine receptors (nAChRs) [46], suggests a mechanism by which nicotine may prevent stress-induced impairment of memory and LTP. Moreover, the observation that stress-induced atrophy of hippocampal neurons reversibly impairs cognitive function, suggests that chronic nicotine treatment may reduce the negative impact of excitotoxic amino acids and corticosteroids, and subsequently, prevent permanent damage and cognitive decline.

The combined effects of psychosocial stress and nicotine in AD have not been studied thoroughly in any AD animal model; hence this review summarizes recent findings that are largely reported from this laboratory.

2. THE Aβ RAT MODEL OF AD

A number of neuropathological features of AD have been reproduced in mice by the introduction of APP, PS1, and PS2 transgenes [47-51]. The majority of transgenic mice exhibit cognitive deficits, amyloid peptides accumulation, and synaptic dysfunction, without showing neurofibrillary tangle formation, neuronal death, or microglial activation [52-55]. The establishment of double or triple-transgenic mice has improved the phenotypic similarities between animals and humans [56,57]. However, certain major limitations of transgenic mouse models of AD have been recognized. For example, the cerebrospinal fluid of these AD models contains a constant, high concentration of various Aβ peptides, thus complicating investigation of the molecular bases of synaptic dysfunction. Additionally, the lack of neuronal death suggests that compensatory factors may be triggered by the introduction of transgenes into these mice [58].

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 the human AD pathology. However, studies involving exogenous administration of Aβ have reported neurodegeneration and microglial activation, proximal to Aβ deposits [50, 60]. Exogenous Aβ administration model of AD is not without limitations. For example, injection/infusion of Aβ peptides is an invasive procedure, particularly when using osmotic pumps. The injury at the site of infusion may contribute 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.

During normal cellular metabolism, neurons secrete low levels of soluble Aβ peptides into cerebrospinal fluid and plasma [61, 62]. These peptides and their precursor, APP may have a physiological role in synaptic structure and function [63]. It has been suggested that the extent and rate at which the pool of soluble Aβ oligomers accumulates is dependent on the rates of Aβ catabolism and clearance [62, 64-66]. The Aβ rat model was established by continuous osmotic pump infusion of a mixture of $Aβ_{1-40}$ and $Aβ_{1-42}$ (300

pmol/day) for 14 days. Control rats were similarly infused with the non-toxic reverse peptide $Aβ_{42-1}$ [18-21].

3. CHRONIC STRESS INTENSIFIES COGNITIVE DEFICITS

The radial arm water maze (RAWM) is a hybrid of the radial arm maze and the Morris water maze; it combines the variable spatial complexity of the radial arm maze with the rapid motivated learning of the Morris water maze while minimizing their disadvantages. It is a reliable and sensitive behavioral test for analyzing hippocampus dependent learning and memory [67-69].

Seven experimental groups were designated as control, stress, nicotine, Aβ, nicotine/Aβ, stress/Aβ and nicotine/stress/Aβ. The stress and stress/Aβ groups were subjected to daily stress for 6 weeks and the Aβ and Aβ/stress groups were infused with a mixture of $Aβ_{1-40}$ and $Aβ_{1-42}$ (300 pmol/day) during the fifth and sixth week. The control and stress groups were infused with $Aβ_{42-1}$, an inactive reverse peptide. The RAWM training protocol consisted of a learning phase of four 1-min consecutive learning trials-followed by a short-term and a long-term memory tests, 20 min and 24 hr, respectively, after the last learning trial. The animals had to locate a black platform submerged 1 cm below the water level near the end of one of the 6 swim arms, This procedure was conducted for a minimum of 8 consecutive days or until the rat satisfied a condition called days to criterion (DTC), which 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 memory tests [18-21, 70, 71].

Days 6-8 of testing in the radial arm water maze clearly showed the significantly impaired ability of the stress/Aβ rat group to learn compared to all other groups including the Aβ group. For example, in trial 4, 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 rat groups [18-20]. Chronic nicotine treatment (1 mg/kg/12 hr) completely prevented the effect of Aβ and the combination of Aβ and stress [20]. Neither chronic stress alone nor nicotine alone had a significant effect on learning, which is in agreement with our previous findings [72]. The effects on the learning curve were confirmed in the DTC test. 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. Fig. (**1A**) [20].

Short-term memory was significantly impaired in both the stress and Aβ groups. However, the stress/Aβ group showed significantly greater impairment of short-term memory than all other groups. These results were further confirmed by the DTC test for short-term memory, which showed that although the Aβ and stress groups required significantly more days to reach the criterion than control, the stress/Aβ group required significantly more days than these two groups Fig. (**1B**) [18]. The deficits in stress, Aβ and stress/Aβ groups were prevented in all nicotine-treated groups (nicotine/stress, nicotine/Aβ and nicotine/stress/Aβ groups [18, 19]).
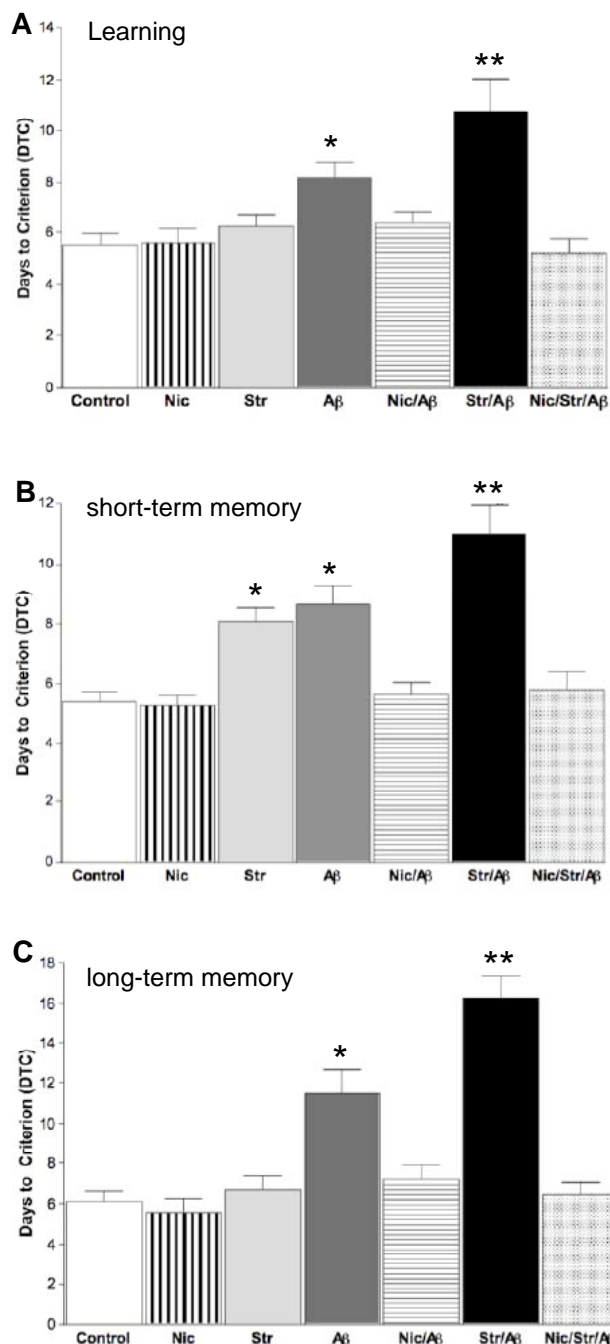
Fig. (1). Days to criterion (DTC) values; criterion is reached when a rat makes a maximum of one error per three consecutive days of testing in the RAWM. Chronic nicotine treatment prevents stress-exacerbated impairment of learning, short-term, and long-term memory in Aβ rats. (**A**) Memory function, measured as reaching DTC, indicated that the combination of stress and Aβ impaired learning more than stress or Aβ, alone, thus requiring stress/Aβ rats to be trained for a minimum of 17 days in the RAWM in order to reach criterion. Neither nicotine, nor stress, alone, affects acquisition or long-term memory performance (**C**). Chronic nicotine treatment significantly prevents stress exacerbated Aβ-impairment of short-term (**B**) and long-term memory (**C**). All values are mean $\pm$ S.E.M. (n=12-15 rats/group); *p<0.05 compared to control and nicotine-treated groups; **p<0.05 compared to all groups. Modified from references [18, 20].

The 6-week psychosocial stress paradigm impairs short-term memory but does not impair learning or long-term memory in normal rats [18, 73]. However, infusion of Aβ in chronically stressed rats (stress/Aβ group) caused a severe impairment of long-term memory [20] that was significantly greater than that caused by Aβ infusion alone Fig. (**1C**). Again, nicotine prevented the effects of Aβ and stress/Aβ on long-term memory Fig. (**1C**) [20].

4. CHRONIC STRESS EXACERBATES IMPAIRMENT OF SYNAPTIC PLASTICITY IN AD MODEL

To relate cognitive deficit to possible changes in the cellular substrate of memory, we evaluated synaptic plasticity in area CA1 of the hippocampus. We recorded population spikes (pSpike) from area CA1 of anesthetized rats and determined changes in the slope of field excitatory postsynaptic potential (fEPSP: a measure of synaptic strength) and pSpike amplitude (a measure of the number of neurons firing action potentials) [72]. In these electro-physiological experiments, we first assessed basal synaptic function by applying a range of stimulus intensities to generate input-output (I/O) curves for all seven groups of animals. The I/O curves of Aβ and stress/Aβ groups showed a significant rightward shift compared with those of control and stress groups indicating impaired basal synaptic transmission in animals infused with Aβ [18]. Chronic treatment with nicotine prevented impairment of basal synaptic transmission in these groups [18].

4.1. Early Phase Long-Term Potentiation (E-LTP)

E-LTP is believed to be a cellular correlate of short-term memory [74]. High frequency stimulation (HFS) in control rats induced a robust E-LTP, which lasted up to 3 hrs after HFS. However, in the stress, Aβ and stress/Aβ animals, the maximum increase in the response 5 min after HFS, was only about 50% of that of the control animals Fig. (**2A**) [18]. The E-LTP magnitude, measured as fEPSP or pSpike amplitude, in these 3 groups gradually decayed such that, at 60 min post-HFS the fEPSP slope of the stress/Aβ group was not different from that of the base line, thus, was significantly lower than those of the other groups including the stress and the Aβ groups [18, 19]. In the nicotine treated Aβ and stress/Aβ rats, E-LTP was not significantly different than those of the control or nicotine alone groups Fig. (**2A**).

4.2. Late Phase LTP (L-LTP)

L-LTP, evoked by multiple-train HFS, was so severely impaired in the stress/Aβ rats that at 5 hr after HFS, the slope of fEPSP was significantly lower than the baseline Fig. (**2B**) [21]. The magnitude of L-LTP of animals of the Aβ group was significantly lower than that of control group. The magnitude of L-LTP of the three nicotine treated rat groups (nicotine, nicotine/stress/Aβ and nicotine/Aβ) was not significantly different than that of the control group. Thus, nicotine prevented the Aβ-induced impairment of synaptic plasticity. It is interesting to note that although stress markedly accentuates the effect of Aβ infusion, it has no significant effect on L-LTP in normal animals [7] as we have reported earlier Fig. (**2B**) [11, 21, 73, 75].
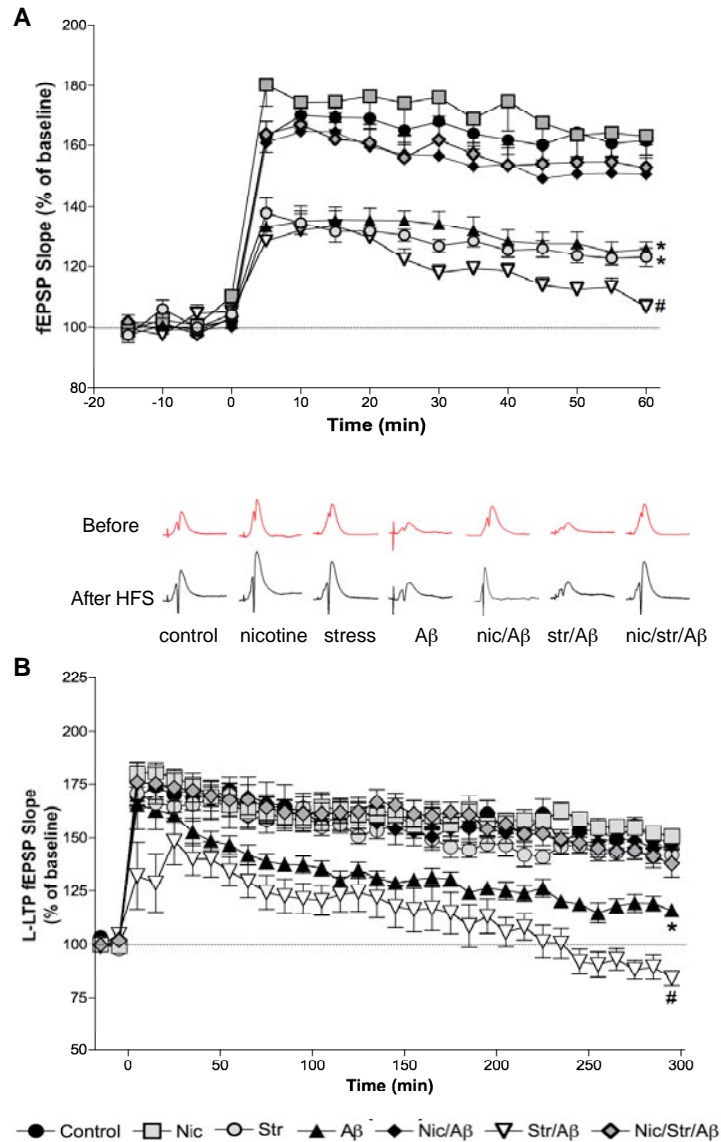
Fig. (2). Hippocampal long-term potentiation (LTP) of the CA1 region evoked by repetitive stimulation (applied at t=0) of the Schaffer collaterals/commissural pathway and measured as increases in the slope of fEPSP in urethane-anesthetized rats. (**A**) Early phase (E-LTP), evoked by high frequency stimulation (HFS), was significantly decreased in stress and/or Aβ groups. Chronic nicotine treatment significantly prevented stress-induced E-LTP suppression in Aβ rats. (**B**) Late-phase (L-LTP), evoked by multiple high frequency stimulation (MHFS), was significantly decreased in the Aβ and stress/Aβ groups. Chronic nicotine treatment prevented the effects of both stress and/or Aβ. Values are mean $\pm$ S.E.M. from 5-8 rats (*$p<0.05$ compared to control animals; #$p<0.05$ compared to all animals). Insets are traces from representative experiments. Modified from references [18, 19].

4.3. Long-Term Depression (LTD)

Just as high levels of synaptic activity potentiate synaptic transmission, low levels of persistent stimulation depress hippocampal synapses. Thus, to examine the mechanism responsible for stress and/or Aβ-mediated impairment of LTP, we examined the magnitude of n-methyl-d-aspartate (NMDA)-dependent LTD expressed in the Schaffer collaterals pathway using paired pulse protocol in anesthetized animals [21, 72, 75]. All animal groups displayed robust LTD, which was measured as decreases in the slope of fEPSP. Chronic stress or Aβ- infusion, alone, caused a significantly greater reduction in synaptic strength than that seen in control animals. The magnitude of LTD in stress/Aβ animals was significantly greater than that in control, stress, and Aβ animals. Chronic nicotine administration prevented the effect of stress and/or Aβ on LTD and restored the synaptic signal to a magnitude comparable to that of control animals [21].

5. CHRONIC STRESS ACCENTUATES ALTERED LEVELS OF SIGNALING MOLECULES ESSENTIAL FOR MEMORY AND SYNAPTIC PLASTICITY

Calcium calmodulin kinase II (CaMKII) plays a critically important role in the memory and LTP processes. 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 [76] and anesthetized animal hippocampi [9, 11, 18]. Activation of NMDA receptor causes a transient increases in intracellular calcium concentrations leading to autophosphorylation of CaMKII [77]. The rapid autophosphorylation of CaMKII results in a constitutively active CaMKII [78] that phosphorylates and activates α-amino-3-hydroxy-5-methyl-4-isoxazole (AMPA) receptors and the synaptic vesicle-specific protein, synapsin, which are important for LTP expression [76,79,80]. It is proposed that activation of CaMKII serves as a molecular switch that converts transient Ca^{2+} signals into long lasting biochemical changes that trigger synaptic plasticity [81].

To further elucidate the potential mechanism by which stress exacerbated Aβ-induced impairment of cognitive abilities and synaptic plasticity, we evaluated the effect of chronic stress and Aβ on the basal levels of signaling molecules essential for these processes by immunoblot analysis. Table **1** summarizes the results of these experiments.

5.1. Basal Levels of CaMKII and Calcineurin

Although chronic stress or Aβ markedly reduced the basal levels of phosphorylated CaMKII, these levels were significantly more reduced in the CA1 of stress/Aβ animals Fig. (**3A**) [18]. In normal animals, nicotine did not change the basal levels of this enzyme, but it completely prevented the effect of stress, Aβ or stress/Aβ on the levels of CaMKII Fig. (**3A**) [20].

Phosphorylated 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 [82]. Immunoblot analysis revealed significant increase in the basal levels of calcineurin in the stress, Aβ and stress/Aβ groups compared to those of the control group Fig (**3B**) [18, 21] and that nicotine treatment normalized calcineurin levels in these animals Fig. (**3B**) [21].

5.2. Basal Levels of CREB and CaMKIV

cAMP response element-binding protein (CREB) signaling, a necessary component for hippocampus-dependent long-term memory formation in mammals [83, 84], is severely compromised by Aβ [85]. We measured basal levels of phosphorylated and total (phosphorylated and non-phosphorylated) CREB. Although the basal levels of p-CREB were significantly reduced in the Aβ and stress/Aβ groups, the levels of total CREB were unchanged in these groups [20]. The ratio of basal protein levels of p-CREB to t-CREB was significantly ($p<0.05$) decreased in Aβ rats, and stress/Aβ rats, compared to control rats Fig. (**4A**) [20]. The decreases in the ratio of p-CREB:t-CREB correlated with reduced phosphorylation of CREB. Furthermore, that the ratio of p-CREB to t-CREB was significantly higher in nicotine/Aβ and nicotine/stress/Aβ rats compared to Aβ and stress/Aβ rats, but not significantly different from control rats, suggested that chronic nicotine treatment prevented Aβ- and stress/Aβ-induced inhibition of CREB phosphorylation [20].

During expression of L-LTP, there is an increase in the basal levels of CaMKIV, which directly phosphorylates CREB [86]. We reported that basal levels of CaMKIV were significantly reduced in Aβ animals and stress/Aβ animals, compared to control animals [20]. By contrast, six weeks of chronic nicotine treatment normalized the basal levels of CaMKIV in these two groups. The basal levels of CaMKIV in nicotine, stress, nicotine/Aβ, and nicotine/stress/Aβ animals were not significantly different from control animals [20].

5.3. Basal Levels of Brain Derived Neurotropic Factor (BDNF)

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 [87]. A possible role for nicotine-mediated neuroprotection has been suggested by studies showing that nicotinic receptor activation increases the levels of neurotrophic factors, including BDNF [88]. Since BDNF plays a major role in neuronal survival [89], we examined

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Table 1.   **Summary of the Effects of Nicotine and/or Stress on the Basal Levels of Essential Signalling Molecules in CA1 Area of the Hippocampus in Aβ-Treated Rats Compared to Control. ⇓Decreased, ⇑ Increased, ⇔ No Change**

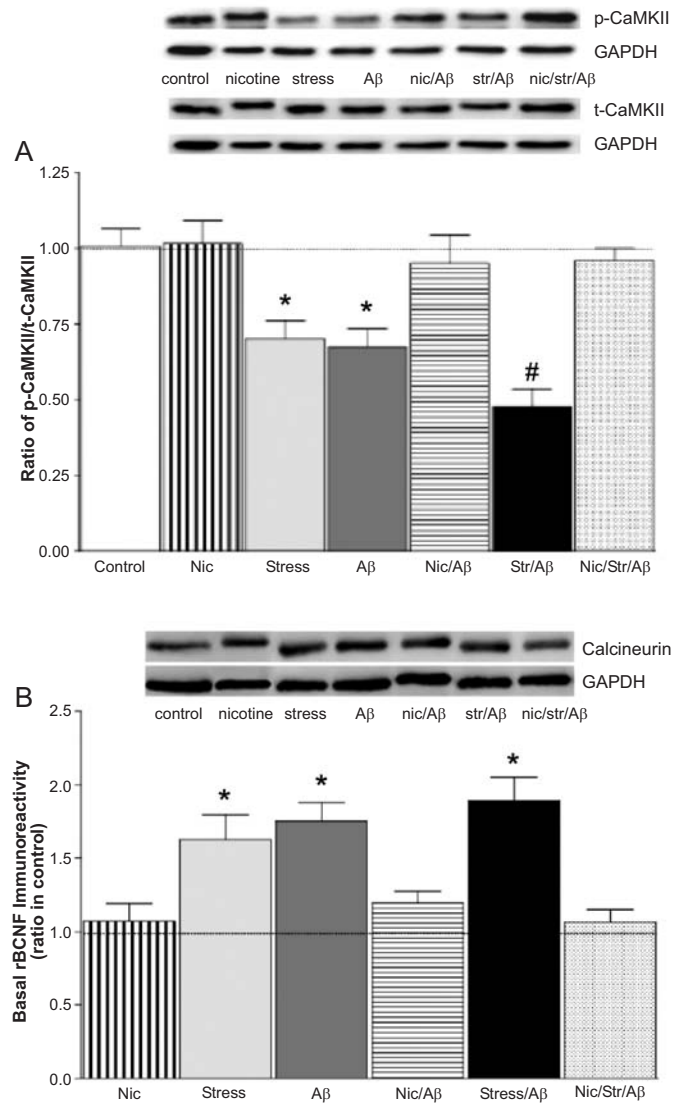|	Nicotine	Stress	Aβ	Nic/Aβ	Str/Aβ	Nic/Str/Aβ
p-CaMKII	⇔	⇓	⇓	⇔	⇓	⇔
t-CaMKII	⇔	⇔	⇔	⇔	⇔	⇔
Calcineurin	⇔	⇑	⇑	⇔	⇑	⇔
BDNF	⇑	⇔	⇑	⇑	⇑	⇑
p-CREB	⇔	⇔	⇓	⇔	⇓	⇔
t-CREB	⇔	⇔	⇔	⇔	⇔	⇔
CaMKIV	⇔	⇔	⇓	⇔	⇓	⇔

Fig. (3). (**A**) Ratio of basal levels of phosphorylated-calcium-calmodulin-dependent protein kinase II (p-CaMKII) to total (t)-CaMKII in CA1. Values are mean $\pm$ S.E.M. from 5-7 rats/group (*$p<0.05$ compared to control and nicotine-treated animals; #$p<0.05$ compared to all groups). (**B**) Basal levels of calcineurin in area CA1. Nicotine prevents the adverse effect of chronic stress on Aβ-induced increases in basal calcineurin levels in hippocampal homogenates. Values are mean $\pm$ S.E.M. from 5-7 rats (*$p<0.05$ compared to control and nicotine-treated animals (nicotine, nicotine/Aβ, nicotine/stress/Aβ). *Insets:* representative immunoblot images. Modified from references [18, 19].

the protein expression of BDNF in the seven groups of rats. Immunoblot analyses revealed significantly ($p<0.05$) higher levels of BDNF in Aβ and stress/Aβ rats, compared to control rats Fig. (**4B**) [20]. The increased basal protein levels of BDNF in area CA1 of Aβ-infused rats is in agreement with an earlier report that shows an increase in the protein levels of BDNF in the forebrain in APPsw mice [90].

That we have detected an increased level of BDNF protein in an area heavily susceptible to Aβ toxic effects is in line with the role of BDNF in the maintenance and repair of neurons [91] and suggests that in early AD, a compensatory mechanism is activated to protect neurons from Aβ-induced neurotoxicity. Furthermore, as chronic nicotine treatment is known to upregulate BDNF protein level and mRNA expression in area CA1 [9, 90], it is not surprising that

BDNF protein levels are significantly increased in nicotine, nicotine/Aβ, and nicotine/stress/Aβ rats, compared to control rats Fig. (**4B**). This finding is in agreement with earlier reports showing that chronic nicotine treatment increased BDNF protein levels in APPsw mice [90] and normal rats [9].

We have shown that BDNF levels in stress/Aβ rats are not significantly different from nicotine/stress/Aβ rats [20]. The lack of a significant difference may be due to maximal expression of BDNF in the presence of a chronic disease state. For example, in post-mortem AD brains, BDNF levels have been shown to be significantly higher in the parietal cortex and hippocampus, compared to controls [87]. It is worth mentioning that Hock and colleagues [92] reported a 2-fold decrease in mRNA levels of BDNF in AD postmortem parietal cortex. This suggests that, perhaps, in
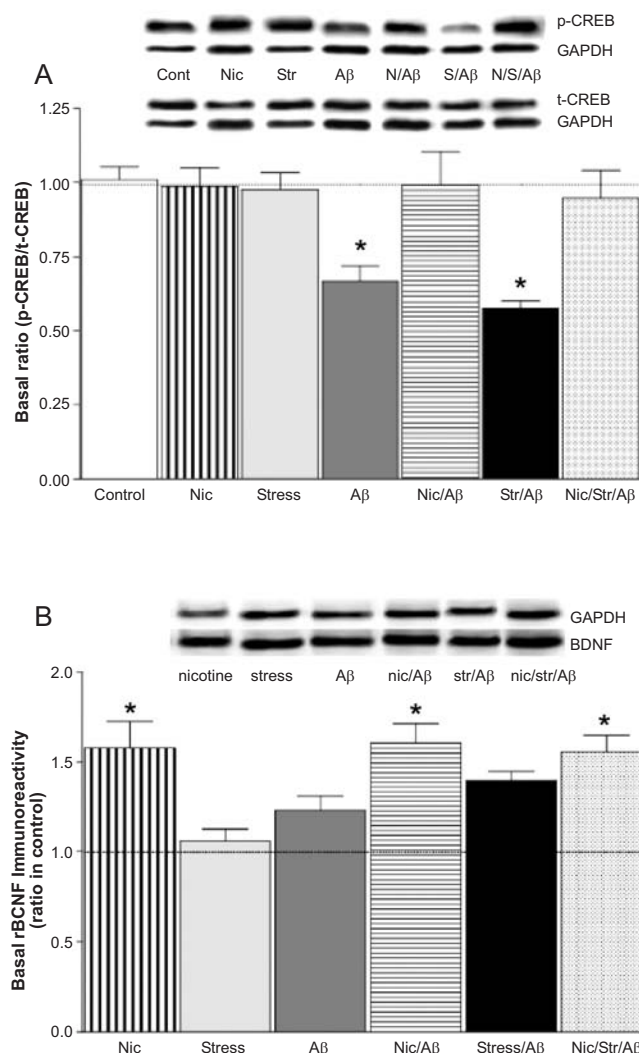
Fig. (4). (**A**) Ratio of basal levels of phosphorylated-cyclic AMP response element binding (p-CREB) to total (t)-CREB in area CA1. Values are mean $\pm$ S.E.M. from 5-7 rats/group (*$p<0.05$ compared to control and nicotine-treated animals). (**B**) Basal levels of brain-derived neurotrophic factor (BDNF) in area CA1. Animals were treated with (-) nicotine or saline for 6 weeks. Groups treated with nicotine showed increased levels of BDNF (Values are mean $\pm$ S.E.M.; n=5-7 rats/group; *$p<0.01$ compared to control animals. Modified from reference [20].

early stages of AD, BDNF protein levels are increased to bring about protection of neuron from the onslaught of the pathogenic peptides and that at later AD stages, BDNF protein levels are decreased. Together, the data suggest that BDNF is involved in the regulation of nicotine-mediated neuroprotection in Aβ and stress/Aβ rats [20].

6. POSSIBLE MECHANISMS OF THE EFFECTS OF STRESS

Previously, we have shown that chronic stress decreases basal levels of p-CaMKII in the CA1 region, and subsequently reduces the magnitude of HFS-induced LTP [11, 19]. Furthermore, the presence of abnormal levels of Aβ peptides disrupts phosphorylation of CaMKII and interferes with LTP induction, as reported in both *in vivo* and *in vitro* studies [19, 93, 94]. Based on findings from our model, we propose that decreasing CaMKII-dependent protein phosphorylation may contribute to the mechanism by

which chronic stress impairs memory and LTP in this model of AD.

In general, activation of mineralocorticoid (type-I) receptor by low levels of corticosteroids produces Ca^{2+} 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 greatly enhances Ca^{2+} influx and inhibits CA1 pyramidal cell excitability [35, 95]. 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 suggesting that Aβ perturbs intracellular Ca^{2+} signaling [26, 96, 97] and inhibits Ca^{2+}-dependent post-translational protein phosphorylation [64]. For example, studies by Zhao *et al.* [94] using acute application of Aβ_{1-42} during HFS showed inhibition of LTP in the dentate gyrus, with corresponding reductions in p-CaMKII levels.

Brain-derived neurotrophic factor plays a major role in neuronal survival [89, 91]. 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 [87, 98]. Earlier reports that show an increase in the protein levels of BDNF in the forebrain in APPsw mice [90] and area CA1 in Aβ-treated rats [19], suggest that in early AD, a protective mechanism may be activated to counter the Aβ-induced neurotoxicity. In contrast, chronic stress has been reported to significantly decrease BDNF levels in area CA1 of the hippocampus [9]. Therefore, by limiting the availability of BDNF, stress interferes with the repair process and consequently 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 [99] suggesting probable neurogenesis [100]. 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 severe reduction in NCAM levels [100, 101]. We speculate that the neurotoxic effect of Aβ in the brain might be initially offset 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 possible mechanism for the stress effect 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 BACE, suggesting that stress is driving the processing of APP toward the amyloidogenic pathway which may account for the increased levels of Aβ [18, 19, 102] and the increased amount of plaque formation [103] that are also observed with stress.

7. POSSIBLE MECHANISM OF THE NEURO-PROTECTIVE EFFECTS OF NICOTINE

Our finding that nicotine reduces amyloid levels [19] is in accordance with reports that nicotine and its metabolites (cotinine) inhibit β-amyloidosis [104-106]. Based on the original "binding surface hypothesis" of Hilbich *et al.* [107] the authors suggest that nicotine and cotinine delay or inhibit β-amyloidosis by non-specifically binding to Aβ and preventing an α-helix to β-sheet conformational conversion [104-106]. It is postulated that nicotine binds to histidine residues (His6 and His13) on the α-helix [104], or to small, soluble β-sheet aggregates [106], and increases the average separation between Aβ monomers in solution, thus delaying the onset of aggregation [106, 108]. Similarly, studies using nornicotine, another nicotine metabolite, demonstrate that nornicotine-based covalent glycation of lysine-16 on the Aβ peptide, occludes the Aβ polymerization domain, and thus, delays formation of the oligomeric β-sheet structure [105]. It is unclear whether nicotine-mediated inhibition of Aβ deposition, aggregation, and/or β-amyloidosis is due to altered processing (towards a non-amyloidogenic Aβ sequence), decreased synthesis, or increased clearance of Aβ peptides. However, a recent study found that chronic

nicotine treatment (1 mg/kg/day and 8 mg/kg/day) reduced rat CSF levels of APPγ, which contains the amyloidogenic Aβ fragment, without significantly altering total soluble APP levels [109, 110]. This suggests that nicotine exerts its effects, in part, by altering the processing of APP away from an amyloidogenic route, towards increased production of APP-carboxyl-terminally truncated forms, which do not contain $Aβ_{1-40}$ and/or $Aβ_{1-42}$. Furthermore, whereas no single mechanism for nicotine-mediated protection has been determined, studies have shown that nicotine increases the levels of neuronal growth factors including BDNF [9, 111, 112], decreases the levels of nitric oxide generated in response to neuronal injury [113], and inhibits glutamate-evoked arachidonic acid release from cultured striatal neurons [114].

Another possible mechanism by which nicotine attenuates the AD-like symptoms is by opposing inflammatory effect of the disease. Inflammatory response is one of the first immune processes in injury. It involves the production of specific molecules that set off the migration of immune cells to wherever the lesion site is, including in the brain. Thus, in stroke, as well as during chronic illnesses, including AD, inflammation takes place in order to clear out and isolate the lesion area. However, sustained inflammation can cause neurotoxicity, which exacerbates the severity of the disease. It is well known that cholinergic anti-inflammatory cascade regulates inflammatory cytokine production through the vagus nerve-dependent pathway involving α7-nicotinic acetylcholine receptor (α7nAChR). Activation of this pathway decreases tumor necrosis factor (TNFα) and blood interleukin-1β levels, inhibits TNF production and reduces pro-inflammatory gene expression. Initiation of this pathway through vagus nerve stimulation or directly by treatment with nicotinic receptor agonists, including nicotine, activates macrophagal α7nAChRs, resulting in anti-inflammatory effects [115-118]. Thus, the α7nAChR-mediated anti-inflammatory action may also contribute to the anti-AD effects of nicotine.

8. SUMMARY

In summary, the presence of chronic stress accentuates the severity of phenotypes in AD rat model. This impairment is likely associated with a number of inter-related disturbances of various signaling molecule pathways including failure of phosphorylated 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 abilities in AD patients and accelerates the progression of the disease.

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