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# NEUROPROTECTIVE EFFECTS OF NICOTINE ON HIPPOCAMPAL LONG-TERM POTENTIATION IN BRAIN DISORDERS

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**Non-standard abbreviations:**

| | |
|---|---|
| AMPAR: | α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors |
| E-LTP: | early-phase LTP |
| fEPSP: | field excitatory postsynaptic potential |
| HFS: | high frequency stimulation. |
| L-LTP: | late-phase LTP |
| MHFS: | multiple high frequency stimulation |
| MLA: | methyllycaconitine |
| nAChR: | nicotinic acetylcholine receptor |
| NMDA: | N-methyl-D-aspartate |
| pspike: | population spike |

**Abstract**

Long-term potentiation (LTP) is commonly considered as the cellular correlate of learning and memory. In learning and memory impairments, LTP is invariably diminished in the hippocampus, the brain region responsible for memory formation. LTP is measured electrophysiologically in various areas of the hippocampus. Two mechanistically distinct phases of LTP have been identified: early-phase LTP (E-LTP; related to short-term memory) and late-phase LTP (L-LTP; related to long-term memory). These two forms can be severely reduced in a variety of conditions and but can be rescued by treatment with nicotine. This report reviews the literature on the beneficial effect of nicotine on LTP in conditions that compromise learning and memory.

## Introduction

Long-term potentiation (LTP) is widely deemed as the cellular correlate of learning and memory. The majority of the LTP studies have been performed in the hippocampus, a bilateral, limbic structure (Teyler and DiScenna, 1986; Sutherland et al., 1989; McNaughton and Foster, 1990]. New information is temporarily stored within the hippocampus before being transferred to the cerebral cortex for long-term storage (Ivanco and Racine, 2000). The role of the hippocampus in learning and memory is supported by direct and convincing evidence from human and animal studies.

Anatomically, the hippocampus is organized in a lamellar fashion and receives highly processed information from widespread neocortical regions. A cross-section of the hippocampus reveals its internal laminar structure with distinct areas, most prominent of which are the pyramidal cells of the Ammon's Horn or Cornu Ammonis (CA1-CA3) subfields, and the granule cell of the dentate gyrus (DG) (Amaral and Witter, 1989; Witter et al., 1989). The hippocampus is characterized by its tri-synaptic circuitry through which information flows in one direction from the entorhinal cortex to area CA1. The perforant path fibers from the entorhinal cortex synapse on the granule cells of the DG. The axons of the granule cells, forming the mossy fiber pathway synapse on the large pyramidal cells of area CA3. The pyramidal cells of area CA3 send the Schaffer collateral nerve fibers to synapse on the pyramidal cells of area CA1 (Amaral and Witter, 1989; Witter et al., 1989). Repetitive stimulation of any of these three presynaptic pathways induces long-lasting changes in synaptic responses of the neurons downstream of that particular pathway. These use-related changes are known as synaptic plasticity, of which LTP is a prime example.

The LTP of DG area is remarkably resistant to insults compared to those of other areas of the hippocampus. This protected status is perhaps due to the fact that the DG area is vital for brain function in that it is one of the few regions of the brain that has the ability for neurogenesis in adulthood. The exact mechanism for this advantaged status of the DG is complex and largely unknown; and seems to be due to a variety of factors that impart this distinction. For example, in the DG area of hypothyroid rat, we have shown a marked decrease in the basal molecular level of the phosphatase calcineurin. Thus, by restricting dephosphorylation, the level of the phosphorylated calcium-calmodulin-dependent protein kinase II (p-CaMKII), a signaling molecule essential for expression of LTP, is maintained. This compensatory mechanism is probably responsible for preservation of LTP in the DG area of the hippocampus (Gerges et al., 2005; 3003). However, in area CA1 of hypothyroid or stressed rats, there is no such compensatory mechanism. Therefore, the decreased level of calcineurin in the DG area of hypothyroid or chronically stressed rats seems to allow ample level of p-CaMKII to sustain the expression of LTP (Gerges et al., 2003, 2005, Gerges and Alkadhi, 2004). However, the mechanism of this remarkable defense in the DG area remains to be determined.

Two mechanistically discrete phases of LTP have been identified: early-phase LTP (E-LTP; related to short-term memory) and late-phase LTP (L-LTP; related to long-term memory). E-LTP is a transient phase that can be evoked by a short period of high frequency stimulation (HFS). It does not require de novo protein synthesis but requires constitutive activation of p-CaMKII, which phosphorylates and enhances the conductivity of glutamate post-synaptic α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPAR) (Fukunaga et al., 1996; Nayak et al., 1996; Lisman et al., 2002). L-LTP is an enduring response

to multiple high frequency stimulation (MHFS) applied over a relatively long period of time. It is a protein synthesis-dependent phase, which requires activation of calcium-calmodulin-dependent protein kinase IV (CaMKIV) and mitogen-activated protein kinase (MAPK) to phosphorylate cAMP-responsive element-binding protein (CREB); and cAMP response element (CRE)-mediated transcription of target genes (Bozon et al., 2003). CRE-mediated gene transcription is absolutely necessary for synapse formation, neuronal survival and long-term memory formation (Snyder et al., 2005).

Both forms of LTP can be measured by electrophysiological techniques in brains of anesthetized animals or in vitro from hippocampal slices. Recordings from anesthetized animals yield two measures; field excitatory postsynaptic potential (fEPSP), which is a synaptic response and population spike (pspike), which represents the number of neurons reaching threshold for action potential.

The cholinergic system in the hippocampus plays a central role in the process of learning and memory. Ample evidence shows that nicotine prevents memory impairments associated with stress (Aleisa et al., 2006a; Tipps et al., 2014), ageing (Arendash et al., 1995; Socci et al., 1995; Levin and Torry, 1996; Grilly et al., 2000; White and Levin, 2004), brain lesions (Decker et al., 1992; Levin et al., 1993b) and cognitive disorders, including Alzheimer's disease (AD) (Sahakian et al., 1989; Wilson et al., 1995; White and Levin, 1999; Newhouse et al., 2001; Srivareerat et al., 2009, 2011; Alkadhi et al., 2010, 2011), schizophrenia (Levin et al., 1996a), attention deficit/hyperactivity disorder (ADHD) (Conners et al., 1996; Levin et al., 1996b; Levin et al., 1998) and Parkinson's disease (Maggio et al., 1997,1998; Newhouse et al., 1997). Although nicotine has been reported in some clinical (Levin et al., 1998) and animal studies (Wesnes and Warburton, 1984; Levin et al.,

1990; Levin et al., 1992, 1993a; Levin et al., 1997) to have memory enhancing abilities in normal subjects, other studies have reported no effect (Dunne et al., 1986; Parrott and Winder, 1989, Aleisa et al., 2006a, b, c) or even memory impairment (Park et al., 2000; Sorenson et al., 1991). The varying results of the effect of nicotine treatment may be due to variations in nicotine dosing, treatment duration, route of administration, and experimental memory task employed.

The effect of nicotine on LTP has been widely studied in animal models of brain disorders (e.g. Kenney and Gould, 2008). Electrophysiological studies reveal that administration of nicotine (acute or chronic) facilitates the induction of LTP in area CA1 of hippocampus by lowering its threshold of induction in slice preparations (Fujii et al., 1999; Fujii et al., 2000; Fujii et al., 2001; Matsuyama et al., 2000) as well as in anesthetized rats (Aleisa et al., et al., 2006a, b, c). The effects of nicotine on memory and LTP are prevented by mecamylamine, a non-selective nicotinic acetylcholine receptor (nAChR) antagonist, indicating that nicotine induces its effects on memory and LTP by acting on nAChRs in the hippocampus (Levin et al., 1987; Levin et al., 1993a; Levin and Torry, 1996; Levin et al., 1997; Fujii et al., 1999; Matsuyama et al., 2000; Levin et al., 2002; Rezvani et al., 2002).

The nAChR belongs to a family of ligand gated ion channels that mediate fast synaptic transmission in the central nervous system (CNS). Structurally, nAChRs are comprised of homologous or heterologous combinations of five polypeptide subunits arranged around a central water-filled pore, like staves of a barrel. Each subunit is composed of four transmembrane (TM1-4) domains. The extracellular N-terminal of each of the five subunits may form the agonist binding (receptor) site (Cooper et al., 1991). Three rings of negative charges, positioned along the inner pore of the channel, constitutes the cationic selectivity of

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nAChR. The nAChRs can be of three major classifications based on their pharmacological and physiological properties*:* the heteropentameric nAChRs (α, β, δ, σ, ε), which exist in endplates of skeletal muscles, the standard neuronal nAChRs formed from α and β combinations, and the homopentameric nAChRs, formed from α7 or α9 subunits (Colquhoun and Patrick, 1997). The hippocampus contains a large number of nAChR subtypes; however, based on electrophysiological and in situ hybridization studies, the heteropentameric α4β2 and homopentameric α7 nAChR subtypes are the most abundant receptor subtypes in the hippocampus (Wada et al., 1989; Seguela et al., 1993).

Nicotine activates presynaptic nAChRs on the Schaffer collateral nerve terminals in area CA1 resulting in increased release of glutamate and the consequent pyramidal cell excitation. Moreover, chronic nicotine treatment upregulates α4β2 and α7 nAChR subtypes in most brain regions including the hippocampus (Ridley et al., 2001; Mugnaini et al., 2002; Parker et al., 2004). The effects of nicotine on memory and LTP are blocked by the α4β2 nAChRs antagonist dihydro-β-erythroidine (Bancroft and Levin 2000; Fujii et al., 2000; Levin and Rezvani 2000; Arthur and Levin 2002), suggesting that nicotine improves memory and LTP by activation of nAChRs, mainly the α4β2 subtypes.

The involvement of α7-nAChRs in memory and LTP is debatable. Whereas blocking α7-nAChRs by methyllycaconitine (MLA) impairs memory and inhibits nicotine action on memory in the radial arm maze (Levin and Rezvani, 2000; Bettany and Levin, 2001; Levin et al., 2002), MLA facilitates the generation of LTP in hippocampal slices (Fujii et al., 2000). The MLA-induced facilitation of LTP is explained by the finding that chronic nicotine treatment induces desensitization of α7-nAChRs in GABAergic interneurons, which reduces the release

of gamma-aminobutyric acid (GABA) from these interneurons, hence indirectly promoting pyramidal cell excitability (Alkondon et al., 2000a, 2000b). Consequently, LTP expression is facilitated by lowering its threshold of induction (Fujii et al., 1999, 2000a, 2001).

Therefore, changing the dynamics of nAChR activation and distribution influences the release of neurotransmitters and affects memory and activity-dependent synaptic plasticity. Furthermore, in addition to modulating the activity of neuronal circuits in hippocampal and cortical brain regions, nAChRs appear to be involved in neuronal survival. For example, in the brains of old mice that lack β2-nAChRs, Xu et al., reported astrogliosis, and microgliosis with neocortical hypertrophy and hippocampal neuronal loss resulting in impaired spatial learning (Xu et al., 1999).

In this review, the neuroprotective effects of nicotine on LTP in certain brain disorders is recounted with emphasis on electrophysiological work reported from my laboratory.

**Alzheimer's disease**

Alzheimer's disease (AD) is characterized by dysfunctional cholinergic mechanisms as is common in some other dementia disorders (Kasa et al., 1997; Perry et al., 2000). Examination of neocortical and hippocampal regions in brains of AD patients reveals a marked loss of α7- and α4β2-nAChRs (Pettit et al., 2001; Auld et al., 2002; Lahiri et al., 2002; Utsuki et al., 2002; Mattson, 2004) and of pre-synaptic terminals in neocortical and hippocampal regions (Terry et al., 1991; Sze et al., 1997), which are correlated with progressive cognitive decline. We have reported similar loss of nAChRs in an animal model of AD (Srivareerat et al., 2011). Immunohistochemical, biochemical, and pharmacological

data suggest that the high affinity binding of the neurotoxic protein $A\beta_{1-42}$ to $\alpha$7- and $\alpha4\beta2$-nAChRs has an important role in AD pathogenesis, including formation of extracellular amyloid plaques and deterioration of cholinergic neurons (Wang HY et al., 2000b; Wang HY et al., 2000a; Ikonomovic et al., 2009). It has been proposed that chronic stimulation of $\alpha$7-nAChRs by $A\beta_{1-42}$ protein accelerates disorder of ERK2-MAPK signaling pathway (Dineley et al., 2002), promotes internalization and intracellular accumulation of $A\beta_{1-42}$ (Nagele et al., 2002), interferes with GABAergic signaling (Alkondon et al., 2000a) and/or furthers excessive stimulation of glutamate receptors (Parpura-Gill et al., 1997). Experiments in exogenous Aβ administration, transgenic mice, and gene-targeting mouse AD models demonstrate correlations among excessive Aβ accumulation, impaired nAChR function (Mattson, 2004; Srivareerat et al., 2011) and deficits in learning, memory, and LTP (Cullen et al., 1997; Itoh et al., 1999; Chen et al., 2000; Freir et al., 2001; Srivareerat et al., 2011; Alzoubi et al., 2013). Collectively, the data suggest that Aβ disrupts memory and LTP by impairing nAChR function.

Numerous epidemiological studies have reported a highly significant negative correlation between cigarette smoking and AD (Brenner et al., 1993; Hillier and Salib, 1997; Ulrich et al., 1997; Potter et al., 1999). In laboratory and clinical studies (Emilien et al., 2000; Moreira et al., 2006), nicotine has been shown to improve cognitive function in AD subjects (Potter et al., 1999) and attenuate Aβ-induced amnesia in rodent models of AD (Newhouse et al., 1988; Maurice et al., 1996; Srivareerat et al., 2011; Gao et al., 2014). Although the mechanism of the neuroprotective effects of nicotine is unknown, one possibility might involve the desensitization and upregulation of nAChRs induced by chronic exposure to the drug.

In Aβ-treated rat models of AD, both E-LTP and L-LTP are severely suppressed as measured by extracellular recording from brains of anesthetized animals (Srivareerat et al., 2009; 2011; Chen et al., 2010; Alkadhi et al., 2011). However, chronic nicotine treatment (1mg/kg s.c. twice per day for 6 weeks prior and during Aβ-infusion) completely prevents the deleterious effects of Aβ on both E-LTP and L-LTP of CA1 (Fig 1) (Srivareerat et al., 2009; 2011; Alkadhi et al., 2011) and DG areas of the hippocampus (Alkadhi, 2018). Comparable results have been reported in streptozotocin model of AD in anesthetized rats where chronic nicotine also prevents inhibition of LTP in area CA1 (Esteves et al., 2017). In area CA1 slices from Aβ treated rats, nAChR agonists completely preserve E-LTP and L-LTP (Kroker et al., 2013).

In contrast to the preponderance of published reports, some laboratories reported that nicotine neither enhances nor depresses stimulation-induced LTP in normal animals (Freir et al., 2001; Itoh et al., 1999). For instance, Itoh et al. report that in slices from Aβ-infused rats, perfusion of 50 mM of nicotine for 10 min diminishes population spike amplitude in area CA1 of control rats. In similar studies, Freir et al. report that injection of nicotine and Aβ, 1 hour before HFS, diminishes LTP much more than does Aβ alone.

**Mental Stress**

Stress ranges from mild to post-traumatic stress disorder (PTSD) and negatively affects normal brain structure and function (McEwen 2000). The hippocampus is highly sensitive to damage during repeated stress (Sapolsky 1993, 2000; Smith 1996). Chronic psychosocial stress impairs hippocampus-dependent learning and memory in animal models (Holscher 1999; Park et al., 2000; Gerges et al., 2004a) and in humans (Lupien et al.,

1997). Additionally, stress markedly inhibits LTP of area CA1 of the hippocampus in anesthetized rats (Gerges et al., 2001) and in hippocampal slices (Foy et al., 1987). However, in the DG area the great majority of reports show no impairment (Bramham et al., 1998; Gerges et al., 2001; Alkadhi, 2018: but see Vereker et al., 2001).

The mechanism of impairment of memory and LTP by stress is not well understood. A suggested contributing mechanism is the increased levels of excitatory amino acids and glucocorticoids during stress (Watanabe et al., 1992a; Magarinos and McEwen 1995). Elevation of excitatory amino acids and glucocorticoid levels during stress is known to induce hippocampal atrophy and promote neuronal death due to excitotoxicity (Watanabe et al., 1992a, b; Magarinos and McEwen 1995; Magarinos et al., 1996; McEwen 1997).

Stress and stress hormones downregulate nAChRs and impair memory (Pauly and Collins, 1993; Diamond et al., 1994; Luine et al., 1994; Takita and Muramatsu, 1995; Takita et al., 1999; Gerges et al., 2001, 2004b; Aleisa et al., 2006c). The finding that chronic nicotine treatment prevents stress-induced downregulation of nAChRs (Takita et al., 1999; Srivareerat et al., 2011), suggests a possible mechanism by which nicotine exerts its neuroprotective effects on stress-induced impairment of memory and LTP. Stress-induced atrophy of hippocampal neurons (e.g. Schoenfeld et al., 2017; Gilabert-Juan et al., 2016) results in impairment of cognitive function, which suggests that chronic nicotine treatment may reduce the impact of excitotoxic amino acids and glucocorticoids, thus, preventing permanent damage and cognitive decline. From this lab, we report that chronic psychosocial stress severely diminishes E-LTP in hippocampal area CA1, without affecting that of the DG area (Gerges et al., 2001,2004a; Aleisa et al., 2006 b, d), a hippocampal region known to be resistant to a variety of insults. On the other hand, chronic nicotine treatment completely

prevented the stress-induced impairment of E-LTP (Aleisa et al., 2006 b, d). Interestingly, we show that acute bolus nicotine treatment fails to reverse the deleterious effects of stress on E-LTP (Aleisa et al., 2006d).

**Co-occurrence of Alzheimer's disease and chronic stress**

Chronic stress exacerbates the severity of cognitive decline in a variety of disorders (Vanitallie, 2002), including Cushing's syndrome (Starkman et al., 1999), PTSD (Yehuda, 2001), hypothyroidism (Gerges et al., 2001; Gerges et al., 2004b), depression (McEwen, 1999; Meyer et al., 2001) as well as AD (Srivareerat et al., 2009; , 2011, Tran et al., 2011a, b). The physiological consequences of stress depend on the intensity and duration of the stressor and upon how the organism perceives and reacts to the noxious stimulus (Gold et al., 1984; Diamond et al., 1992; Joels, 2006).

Chronic stress is a serious risk factor for AD (Wilson et al., 2003; Wilson et al., 2005, Tran et al., 2010, 2011a, b) since elevated glucocorticoid levels are correlated with increased Aβ deposition (Kulstad et al., 2005; Green et al., 2006), enhanced Aβ-mediated neurotoxicity, and accelerated cognitive decline (Aisen et al., 2000; Pedersen et al., 2006; Srivareerat et al., 2009, 2011, Alkadhi et al., 2010a, 2011;Tran et al., 2010, 2011a,b). In AD, the presence of stress may further reduce the ability of neurons to survive coincident insults, thus intensifying Aβ-mediated neurotoxicity and impairment of memory and synaptic plasticity (Foy et al., 1987; Shors et al., 1990; Diamond et al., 1992; Shors and Thompson, 1992). Therefore, any exposure to stress is a threat to cellular metabolic activity and CNS function.

We studied the effect of chronic psychosocial stress in a preclinical (at-risk) model of AD (subAβ model). This model involves infusion of subtoxic dose of Aβ1-42 peptide that does not affect normal cognition or synaptic plasticity (Tran et al., 2010,2011a, Alkadhi and Tran,

2014a). In area CA1 of chronically stressed preclinical (Stress/subAβ) AD model, E-LTP is more severely diminished than with stress alone. The effect of stress on L-LTP of hippocampal area CA1 of this model is even more dramatic; although neither stress nor subAβ model alone affects L-LTP, the combination of the two conditions produces a marked depression of this form of synaptic plasticity. Even in the insult resistant DG area, the combination of chronic stress and subAβ severely impacts E-LTP, while having no effects on L-LTP of the same area.

In the full toxic dose of our Aβ rodent model, E-LTP of area CA1 in the Aβ treated stressed rat (stress/Aβ) is more severely blocked than those treated with either Aβ or stress alone. Chronic nicotine treatment completely prevents the effects of the combination (fig 1A). Similarly, in area CA1 the L-LTP of stressed/Aβ rat is more severely blocked in the combination treatment than that with Aβ treatment alone and nicotine totally prevented the effect of the combination. We also studied the effect of the combination on DG area in the same model. The effect of the combination on E-LTP in the stress-resistant DG area is not significantly different than that of the Aβ treatment alone (Alkadhi, 2018). However, the effect of the combination on L-LTP of the DG is markedly more severe than that of the Aβ treatment alone and is prevented by chronic treatment with nicotine (Alkadhi, 2018).

**Hypothyroidism**

Thyroid disorders are the second most common endocrine disorder in the United States, with an increased prevalence in elderly (Helfand and Crapo, 1990; Elliott, 2000; Hueston, 2001). Hypothyroidism is an endocrine disorder characterized by reduced normal levels of thyroid hormone (thyroxin, T4). When it develops during infancy or early childhood, hypothyroidism results in cretinism, which is characterized by impaired

development of skeletal system and central nervous system resulting in severe mental retardation among other symptoms (David and Nathaniel, 1983; Porterfield and Hendrich, 1991; Porterfield, 1994; Rovet, 1999).

Adult-onset hypothyroidism displays a wide range of CNS dysfunctions including severe cognitive impairments manifested as inability to concentrate, slow mentation and poor memory for recent events (Haggerty et al., 1990; Mennemeier et al., 1993; Leentjens and Kappers 1995; Burmeister et al., 2001). Older adults with hypothyroidism show impairment of learning, visual-spatial relationship abilities, and attention (Osterweil et al., 1992).

In experimental animals, we have shown that hypothyroidism severely impairs learning as well as short-term and long-term memory in adult rats (Gerges et al., 2004b; Alzoubi etal., 2006b). Synaptic plasticity impairment has been also reported in hypothyroidism. Hippocampal E-LTP is shown to be impaired during hypothyroidism at the neonatal stages (Niemi et al., 1996; Gilbert and Paczkowski 2003) as well in adulthood (Gerges et al., 2001, 2005; Vara et al., 2003; Alzoubi et al., 2006b). Interestingly, impairment is reported in the pspike amplitude, but not in the fEPSP of E-LTP and L-LTP during adulthood of developmental-onset hypothyroidism (Gilbert 2004; Sui et al., 2005), which suggests impairment of generation of nerve action potentials.

We have reported that hypothyroidism abolishes both E-LTP and L-LTP in area CA1 (Gerges et al., 2001; Gerges and Alkadhi. 2004; Alzoubi et al, 2006a, b; 2007b). However, in hypothyroid animals chronically treated with nicotine, both E-LTP and L-LTP of the CA1 are normal indicating that nicotine protects this area of the hippocampus (Fig 2) (Alzoubi et al, 2006a, b; 2007b). A striking example of the resistance of the DG area to insults is the total

lack of effect of hypothyroidism or hypothyroidism in the presence of chronic stress on both E-LTP and L-LTP of this area as expressed in the effect on the fEPSP or population spike (Gerges et al., 2001; Gerges and Alkadhi. 2004).

**Sleep deprivation**

Sleep is characterized by cyclic occurrence of two major types of sleep: rapid eye movement (REM) and non-REM (slow wave or delta). Studies have shown that in the course of the night, the two sleep stages are expressed and alternate regularly. A night of sleep consists of five to six cycles, each lasting 90 minutes. Although all sleep cycles in a night last about 90 minutes, the duration of each of the two major sleep types in the cycle changes as the night progresses with REM sleep duration increasing and non-REM duration decreasing. The deepest and most restorative sleep occurs during stage 3 (formerly stages 3 and 4) of non-REM sleep, which is characterized by low overall brain activity. In contrast, REM sleep, which starts after non-REM sleep, is characterized by increased brain activity similar to wakefulness. (McCarley, 2007). Each sleep type seems to impact certain memory mode; for instance, non-REM sleep strengthens declarative memory whereas procedural memory is strengthened with REM sleep (Diekelmann and, Born, 2010). Compelling evidence suggests a strong correlation between sleep deprivation (SD) and cognitive impairment in both animals and humans (Polzella, 1975; Youngblood et al., 1997; Smith et al., 1998; McDermott et al., 2003; Guan et al., 2004; Tartar et al., 2006; Ferrara et al., 2008, Alhaider et al. 2010b; 2011, Aleisa et al., 2011a, b; Alkadhi et al., 2012; Zagaar et al., 2012, 2013a). Animal studies of REM SD using the multiple columns-in-water method showed impaired spatial memory

as tested in the Morris water maze and radial arm water maze (fig 3) (Wang et al., 2009; Alhaider et al., 2010b, 2011; Zagaar et al., 2012, 2013a).

Sleep deprivation suppresses both E-LTP and L-LTP in hippocampal area CA1 (McDermott et al., 2003; Kim et al., 2005; Kopp et al., 2006; Tartar et al., 2006; Alhaider et al., 2010b, 2011, Zagaar et al., 2012, 2013a) and DG areas (Marks and Wayner, 2005; Ishikawa et al., 2006; Alhaider et al., 2010a, 2015; Zagaar et al., 2016, 2013b). The negative effect that SD has on synaptic plasticity is believed to be due to detrimental changes in intracellular signaling. For instance, after 24 hours of REM SD, subunit composition and turnover of glutamate N-methyl-D-aspartate (NMDA) receptors, which are critical to LTP induction, are negatively impacted (Chen et al., 2006). Additionally, as brief as 12 hours of SD impairs phosphorylation of hippocampal glutamate AMPARs, which are central in initiating synaptic plasticity signaling (Hagewoud et al., 2010). Molecular studies in the hippocampus have revealed that the expression of important signaling molecules and growth factors (e.g. MAPK, CREB and BDNF) implicated in LTP and memory are reduced after 8, 24 and 48 hours of SD (Guan et al., 2004; Guzman-Marin et al., 2006; Alhaider et al., 2010a, 2011; Zagaar et al., 2012, 2013a, b). Above all, the expression of p-CaMKII is significantly decreased after 24 hours of SD whereas the levels and activity of calcineurin are increased (Wang et al., 2009; Alhaider et al., 2010a, b; Zagaar et al., 2012, 2013b; alkadhi and Alhaider, 2016).

We have also studied the neuroprotective effects of nicotine on E-LTP of the hippocampal DG and CA1 areas in rats REM sleep deprived for 24hr or 48hr. While SD prevents E-LTP expression in both CA1 and DG areas, chronic nicotine treatment completely prevents the deleterious effects of SD on this response (fig 4) (Aleisa et al., 2011a).

Interestingly, even an acute dose of nicotine (1 mg/kg given 3 times during the 24hr SD period) is able to prevent the effects of post-learning SD on long-term memory (Aleisa et al. 2011b). This may suggest that in SD, even acute nicotine can protect L-LTP, which is the cellular correlate of long-term memory.

**Schizophrenia**

Individuals with mental illnesses are particularly likely to be heavy smokers; for example, heavy tobacco use among people with schizophrenia is prevalent (Ziedonis et al., 2008). It has been suggested that this may be a form self-medication to ameliorate common cognitive dysfunction seen in schizophrenia. It is indicated that the cognitive dysfunction and inhibition of synaptic function may be due to excessive schizophrenia-linked neuregulin 1 (NRG1) signaling through its receptor ErbB4. LTP, recorded from area CA1 pyramidal cells in acute hippocampal slices, is significantly reduced in NRG1β treated rats. Chronic nicotine treatment (subcutaneous injection of nicotine; 0.5-1 mg/kg, twice daily for 10-15 days) prevents impairment of LTP in NRG1β treated rats (Yamazaki et al., 2017).

**Other conditions**

Various other conditions where LTP is impaired and brain function compromised have been shown to be restored with nicotine treatment in experimental settings. For example, status epilepticus can cause serious brain damage resulting in cognitive dysfunction including impairment of memory and attention. In experimental convulsive status epilepticus, recordings from acute hippocampal slices show severe impairment of LTP, which is reversed in the presence of nicotine (Xu et al., 2017). Even the effects of aging on cognitive function seem to be reduced with nicotine. Experiments in hippocampal area CA1 slices of aged F44 rats reveal significant decline in synaptic plasticity. These age-related

alterations seem to involve both presynaptic and postsynaptic mechanisms, which may be related to the observed poor spatial memory acquisition and retention in these aged rats (Deupree et al., 1993). The threshold for induction of LTP increases with age. This age-induced impairment of LTP induction is reversed with nicotine treatment (Fujii and Sumikawa, 2001). The age-related inhibition of LTP in the DG is also attenuated by nicotine (Curran and O'Conner, 2002). Environmental contaminants such as the heavy metal Lead can cause marked cognitive impairments in children (Lidsky & Schneider, 2003; Meng et al., 2005) and experimental animals (Lasley & Gilbert, 1999; Ruan et al., 2000). Previous studies have reported that chronic lead exposure during development impairs the induction of LTP in the rat hippocampus (Lasley & Gilbert, 1999; Ruan et al., 2000). Nicotine attenuates deficits in spatial learning in rats chronically exposed to lead (Zhou & Suszkiw, 2004) and rescues LTP (Wang et al., 2006).

**Concluding remarks**

Most reports have shown that nicotine does not improve cognition in healthy animals but seems to have a protective effect against conditions that impair cognitive abilities. Only high doses of nicotine (e.g. 5 mg/kg and higher) have been reported to enhance memory performance of "normal" animals in the radial arm maze task (Bancroft and Levin 2000; Bettany and Levin 2001). However, it has been suggested that environmental conditions, such as noise stress, are necessary for revealing the positive effects of nicotine on memory (Grobe et al., 1998), therefore, since stress impairs short-term memory, which is prevented by nicotine; this neuroprotective effect of the drug may appear as enhancement in these seemingly normal animals.

It has been reported that smokers have a lower risk of developing neurodegenerative diseases and other neuropsychiatric disorders. For example, schizophrenic patients seemingly relieve the symptoms of the disorder with tobacco smoking. Thus, the increase in the rate of tobacco products use during conditions such as chronic stress and schizophrenia could be a self-medication to counteract the harmful effect of these conditions on cognitive function. Therefore, nicotine and nicotine-like compounds have been proposed as potential treatment for neuropsychiatric conditions. These suggestions, however, raise serious ethical issues, because nicotine is a potentially toxic substance and tobacco smoking is a major risk factor for cancers and heart and lung diseases.

In addition to other effects, studies have shown that nicotine increases the levels of neuronal growth factors (Maggio et al., 1997; Belluardo et al., 1998). Among the neuronal growth factors that are affected by nicotine is brain-derived neurotrophic factor (BDNF), which plays a principal role in the expression and support of synaptic plasticity including LTP (Figurov et al., 1996; Ying et al., 2002). BDNF is the most abundant neuronal growth factor in the brain (Webster et al., 2002; reviewed in: Cunha et al., 2010, Machaalani and Chen, 2018). BDNF produces its positive effects on neuronal development, growth and synaptic plasticity through activation of tyrosine kinase receptor B (TrkB) (Fayard et al., 2005), which eventually leads to involvement of cAMP-response-element-binding protein (CREB) to regulate genes expression involved in the expression and support of LTP (Ernfors and Bramham, 2003).

The majority of studies provides strong evidence showing that exposure to nicotine leads to increased brain BDNF levels (Zhang et al., 2010; Suriyaprom et al., 2013; Jamal et al., 2015; Neves et al., 2017; See Machaalani and Chen, 2018 for review). The expression of BDNF

and its TrkB receptor are linked to a7nAChRs where evidence shows BDNF and nAChRs mutually influencing each other (Freedman et al., 1993; Zhou et al., 2004). Thus, the role of BDNF in the neuroprotective effects of nicotine merits further investigation.

In summary, this short review discusses the effects of nicotine on LTP, which is widely considered as a correlate of learning and memory is described. The efficacy of neuroprotective effect of nicotine in preventing LTP impairment associated with a variety of models of disease conditions is discussed. Reports from this lab a well as others have shown that chronic nicotine treatment prevented memory deficits seen in in animal models of AD, stress, hypothyroidism, sleep deprivation, schizophrenia among others, likely by preventing impairment of LTP.

**Authorship contribution:**

Dr. Karm Alkadhi wrote the manuscript

## References

Aisen PS, Davis KL, Berg JD, Schafer K, Campbell K, Thomas RG, Weiner MF, Farlow MR, Sano M, Grundman M, and Thal LJ (2000) A randomized controlled trial of prednisone in Alzheimer's disease. Alzheimer's Disease Cooperative Study. Neurology **54**:588-593.

Aleisa AM, Alzoubi KH, Gerges NZ, and Alkadhi KA (2006a) Nicotine blocks stress-induced impairment of spatial memory and long-term potentiation of the hippocampal CA1 region. Int J Neuropsychopharmacol **9**:417-426.

Aleisa AM, Alzoubi KH, and Alkadhi KA (2006b) Nicotine prevents stress-induced enhancement of long-term depression in hippocampal area CA1: electrophysiological and molecular studies. J Neurosci Res **83**:309-317.

Aleisa AM, Alzoubi KH, Gerges NZ, and Alkadhi KA (2006c) Chronic psychosocial stress-induced impairment of hippocampal LTP: possible role of BDNF. Neurobiol Dis **22**:453-462.

Aleisa AM, Alzoubi KH, and Alkadhi KA (2006d) Chronic but not acute nicotine treatment reverses stress-induced impairment of LTP in anesthetized rats. Brain Res **1097**:78-84.

Aleisa AM, Helal G, Alhaider IA, Alzoubi KH, Srivareerat M, Tran TT, Al-Rejaie SS and Alkadhi KA (2011a) Acute nicotine treatment prevents REM sleep deprivation-induced learning and memory impairment in rat. Hippocampus **2**:899-909.

Aleisa AM, Alzoubi KH, and Alkadhi KA (2011b) Post-learning REM sleep deprivation impairs long-term memory: reversal by acute nicotine treatment. Neurosci Lett **499**:28-31.

Alhaider IA, Aleisa AM, Tran TT, and Alkadhi KA (2010) Caffeine prevents sleep loss-induced deficits in long-term potentiation and related signaling molecules in the dentate gyrus. Eur J Neurosci **31**:1368-1376.

Alhaider IA, Aleisa AM, Tran TT, and Alkadhi KA (2011) Sleep deprivation prevents stimulation-induced increases of levels of P-CREB and BDNF: protection by caffeine. Mol Cell Neurosci **46**:742-751.

Alhaider IA, and Alkadhi KA. (2015) Caffeine treatment prevents rapid eye movement sleep deprivation-induced impairment of late-phase long-term potentiation in the dentate gyrus. Eur J Neurosci **42**:2843-2850.

Alkadhi KA, Alzoubi KH, Srivareerat M, and Tran TT (2011) Chronic psychosocial stress exacerbates impairment of synaptic plasticity in β-amyloid rat model of Alzheimer's disease: prevention by nicotine. Curr Alzheimer Res **8**:718-731.

Alkadhi KA, Alzoubi KH, Srivareerat M, and Tran TT (2012) Elevation of BACE in an Aβ rat model of Alzheimer's disease: exacerbation by chronic stress and prevention by nicotine. Int J Neuropsychopharmacol 1**5**:223-233.

Alkadhi KA, Srivareerat M, and Tran TT (2010) Intensification of long-term memory deficit by chronic stress and prevention by nicotine in a rat model of Alzheimer's disease. Mol Cell Neurosci **45**:289-296.

Alkadhi KA, and Tran TT (2014) Chronic psychosocial stress impairs early LTP but not late LTP in the dentate gyrus of at-risk rat model of Alzheimer's disease. Brain Res **1588**:150-158.

Alkadhi KA (2018) Delayed effects of combined stress and Aβ infusion on L-LTP of the dentate gyrus: prevention by nicotine. In review (Neurosci let)

Alkondon M, Braga MF, Pereira EF, Maelicke A, and Albuquerque EX (2000a) Alpha7 nicotinic acetylcholine receptors and modulation of GABAergic synaptic transmission in the hippocampus. Eur J Pharmacol **393**:59-67.

Alkondon M, Pereira EF, Almeida LE, Randall WR, and Albuquerque EX (2000b) Nicotine at concentrations found in cigarette smokers activates and desensitizes nicotinic acetylcholine receptors in CA1 interneurons of rat hippocampus. Neuropharmacology **39**:2726-2739.

Alzoubi KH, Aleisa AM, and Alkadhi KA (2006a) Molecular studies on the protective effect of nicotine in adult-onset hypothyroidism-induced impairment of long-term potentiation. Hippocampus **16**:861-874.

Alzoubi KH, Aleisa AM, Gerges NZ, and Alkadhi KA (2006b) Nicotine reverses adult-onset hypothyroidism-induced impairment of learning and memory: Behavioral and electrophysiological studies. J Neurosci Res **84**:944-953.

Alzoubi KH, and Alkadhi KA (2007) A critical role of CREB in the impairment of late-phase LTP by adult onset hypothyroidism. Exp Neurol **203**:63-71.

Alzoubi KH, Srivareerat M, Tran TT, and Alkadhi KA (2013) Role of α7- and α4β2-nAChRs in the neuroprotective effect of nicotine in stress-induced impairment of hippocampus-dependent memory. Int J Neuropsychopharmacol **16**:1105-1113.

Amaral DG, and Witter MP (1989) The three-dimensional organization of the hippocampal formation: a review of anatomical data. Neuroscience **31**:571-591.

Arendash GW, Sanberg PR, and Sengstock GJ (1995) Nicotine enhances the learning and memory of aged rats. Pharmacol Biochem Behav **52**:517-523.

Arthur, D and Levin, ED (2002) Chronic inhibition of alpha4beta2 nicotinic receptors in the ventral hippocampus of rats: impacts on memory and nicotine response. Psychopharmacology (Berl). **160**:140-145.

Auld DS, Kornecook TJ, Bastianetto S, and Quirion R (2002) Alzheimer's disease and the basal forebrain cholinergic system: relations to beta-amyloid peptides, cognition, and treatment strategies. Prog Neurobiol **68**:209-245.

Bancroft A, and Levin ED (2000) Ventral hippocampal alpha4beta2 nicotinic receptors and chronic nicotine effects on memory. Neuropharmacology **39**:2770-2778.

Beck SG, List TJ, and Choi KC (1994) Long- and short-term administration of corticosterone alters CA1 hippocampal neuronal properties. *Neuroendocrinology.* **60**:261-272.

Belluardo N, Blum M, Mudo G, Andbjer B, and Fuxe K (1998) Acute intermittent nicotine treatment produces regional increases of basic fibroblast growth factor messenger RNA and protein in the tel- and diencephalon of the rat. Neuroscience. **83**:723-740.

Bettany JH, and Levin ED (2001) Ventral hippocampal alpha 7 nicotinic receptor blockade and chronic nicotine effects on memory performance in the radial-arm maze. Pharmacol Biochem Behav **70**:467-474.

Blanchard DC, Sakai RR, McEwen B, Weiss SM, and Blanchard, RJ (1993) Subordination stress: behavioral, brain, and neuroendocrine correlates. Behav Brain Re*.* **58**: 113-121.

Bozon B, Kelly A, Josselyn SA, Silva AJ, Davis S, and Laroche S (2003) MAPK, CREB and zif268 are all required for the consolidation of recognition memory. Philos Trans R Soc Lond B Biol Sci **358**:805-814.

Bramham CR, Southard T, Ahlers ST, and Sarvey JM (1998) Acute cold stress leading to elevated corticosterone neither enhances synaptic efficacy nor impairs LTP in the dentate gyrus of freely moving rats. Brain Res **789**:245-255.

Brenner DE, Kukull WA, van Belle G, Bowen JD, McCormick WC, Teri L,and Larson EB (1993) Relationship between cigarette smoking and Alzheimer's disease in a population-based case-control study. Neurology. **43**:293-300.

Burmeister LA, Ganguli M, Dodge HH, Toczek T, DeKosky ST, and Nebes RD (2001) Hypothyroidism and cognition: preliminary evidence for a specific defect in memory. Thyroid **11**:1177-1185.

Chen C, Hardy M, Zhang J, LaHoste, GJ, and Bazan NG (2006) Altered NMDA receptor trafficking contributes to sleep deprivation-induced hippocampal synaptic and cognitive impairments. Biochem Biophys Res Commun **340**:435-440.

Chen L, Wang H, Zhang Z, Li Z, He D, Sokabe M, and Chen L (2010) DMXB (GTS-21) ameliorates the cognitive deficits in beta amyloid (25-35(-)) injected mice through preventing the dysfunction of alpha7 nicotinic receptor. J Neurosci Res **88**:1784-1794.

Chen QS, Kagan BL, Hirakura Y, and Xie CW (2000) Impairment of hippocampal long-term potentiation by Alzheimer amyloid beta-peptides. J Neurosci Res **60**:65-72.

Colquhoun LM, and Patrick JW (1997) Pharmacology of neuronal nicotinic acetylcholine receptor subtypes. Adv Pharmacol **39**:191-220.

Conners CK, Levin ED, Sparrow E, Hinton SC, Erhardt D, Meck WH, Rose JE, and March J (1996) Nicotine and attention in adult attention deficit hyperactivity disorder (ADHD). Psychopharmacol Bull **32**:67-73.

Conrad CD, Lupien SJ, and McEwen BS (1999) Support for a bimodal role for type II adrenal steroid receptors in spatial memory. Neurobiol Learn Mem **72**:39-46.

Cooper E, Couturier S, and Ballivet M (1991) Pentameric structure and subunit stoichiometry of a neuronal nicotinic acetylcholine receptor. Nature **350**:235-238.

Cullen WK, Suh YH, Anwyl R, andRowan MJ (1997) Block of LTP in rat hippocampus in vivo by beta-amyloid precursor protein fragments. Neuroreport **8**:3213-3217.

Cunha C, Brambilla R, and Thomas KL (2010) A simple role for BDNF in learning and memory? Front Mol Neurosci **3**

Curran BP, and O'Connor JJ (2003) The inhibition of long-term potentiation in the rat dentate gyrus by pro-inflammatory cytokines is attenuated in the presence of nicotine. Neurosci Lett **344**:103-6.

David S, and Nathaniel EJ (1983) Neuronal changes induced by neonatal hypothyroidism: an ultrastructural study. Am J Anat **167**:381-394.

Decker MW, Majchrzak MJ, and Anderson DJ (1992) Effects of nicotine on spatial memory deficits in rats with septal lesions. Brain Res **572**:281-285.

Deupree DL, Bradley J, and Turner DA (1993) Age-related alterations in potentiation in the CA1 region in F344 rats. Neurobiol Aging **14**:249-258.

Diamond DM, Bennett MC, Fleshner M, Rose GM (1992) Inverted-U relationship between the level of peripheral corticosterone and the magnitude of hippocampal primed burst potentiation. Hippocampus **2**:421-430.

Diamond DM, Fleshner M, and Rose GM (1994) Psychological stress repeatedly blocks hippocampal primed burst potentiation in behaving rats. Behav Brain Res **62**:1-9.

Dineley KT, Bell KA, Bui D, and Sweatt JD (2002) beta-Amyloid peptide activates alpha 7 nicotinic acetylcholine receptors expressed in Xenopus oocytes. J Biol Chem **277**:25056-25061.

Dunne MP, Macdonald D, and Hartley LR (1986) The effects of nicotine upon memory and problem solving performance. Physiol Behav **37**: 849-854.

Elliott, B (2000) Diagnosing and treating hypothyroidism. Nurse Pract **25**: 92-4, 99-105.

Emilien G, Beyreuther K, Masters CL, and Maloteaux JM (2000) Prospects for pharmacological intervention in Alzheimer disease. Arch Neurol **57**:454-459.

Endo Y, Nishimura JI, and Kimura F (1996) Impairment of maze learning in rats following long-term glucocorticoid treatments. *Neurosci Lett* **203**:199-202.

Ernfors P and Bramham CR (2003) The coupling of a trkB tyrosine residue to LTP. Trends Neurosci **26**:171–173

Esteves IM, Lopes-Aguiar C, Rossignoli MT, Ruggiero RN, Broggini ACS, Bueno-Junior LS, Kandratavicius L, Monteiro MR, Romcy-Pereira RN, and Leite JP (2017) Chronic nicotine attenuates behavioral and synaptic plasticity impairments in a streptozotocin model of Alzheimer's disease. Neuroscience **353**:87-97.

Fayard B, Loeffler S, Weis J, Vogelin E, and Kruttgen A (2005) The secreted brain-derived neurotrophic factor precursor pro-BDNF binds to TrkB and p75NTR but not to TrkA or TrkC. J Neurosci Res **80:**18–28.

Fibiger HC (1982) The organization and some projections of cholinergic neurons of the mammalian forebrain. Brain Res **257**:327-88.

Figurov A, Pozzo-Miller LD, Olafsson P, Wang T and Lu B (1996) Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. Nature **381**(6584):706-709.

Freedman R, Wetmore C, Stromberg I, Leonard S, and Olson L (1993) Alpha-bungarotoxin binding to hippocampal interneurons: immunocytochemical characterization and effects on growth factor expression. J Neurosci **13**:1965–1975

Foy MR, Stanton ME, Levine S, and Thompson RF (1987) Behavioral stress impairs long-term potentiation in rodent hippocampus. Behav Neural Biol **48**:138-149.

Fratiglioni L and Wang H X (2000) Smoking and Parkinson's and Alzheimer's disease: review of the epidemiological studies. Behav Brain Res **113**:117-120.

Freir DB, Holscher C, Herron CE (2001) Blockade of long-term potentiation by beta-amyloid peptides in the CA1 region of the rat hippocampus in vivo. Neurophysiol **85**:708-713.

Fujii S, Ji Z, Morita N, and Sumikawa K (1999) Acute and chronic nicotine exposure differentially facilitate the induction of LTP. Brain Res **846**:137-143.

Fujii S, Ji Z, and Sumikawa K (2000) Inactivation of alpha7 ACh receptors and activation of non-alpha7 ACh receptors both contribute to long-term potentiation induction in the hippocampal CA1 region. Neurosci Lett **286**:134-138.

Fujii S, and Sumikawa K (2001) Acute and chronic nicotine exposure reverse age-related declines in the induction of long-term potentiation in the rat hippocampus. Brain Res **894**:347-353.

Fujii S, Jia Y, Yang A, Sumikawa K (1996) Nicotine reverses GABAergic inhibition of long-term potentiation induction in the hippocampal CA1 region. Brain Res. 2000b; 863:259-65.

Fukunaga K, Muller D, Miyamoto E. CaM kinase II in long-term potentiation. Neurochem Int **28**:343-358.

Gao J, Adam BL, and Terry AV Jr (2014) Evaluation of nicotine and cotinine analogs as potential neuroprotective agents for Alzheimer's disease. Bioorg Med Chem Lett **24**:1472-1478.

Gerges NZ, Stringer JL, and Alkadhi KA (2001) Combination of hypothyroidism and stress abolishes early LTP in the CA1 but not dentate gyrus of hippocampus of adult rats. Brain Res **922**:250-260.

Gerges NZ, Aleisa AM, Schwarz LA, and Alkadhi KA (2003) Chronic psychosocial stress decreases in the dentate gyrus: a possible mechanism for preservation of early LTP. Neuroscience **117**:869-874.

Gerges NZ, Aleisa AM, Schwarz LA, and Alkadhi K (2004a) Reduced basal CaMKII levels in hippocampal CA1 region: possible cause of stress-induced impairment of LTP in chronically stressed rats. Hippocampus **14**:402-410.

Gerges NZ, Alzoubi KH, Park CR, Diamond DM, and Alkadhi KA (2004b) Adverse effect of the combination of hypothyroidism and chronic psychosocial stress on hippocampus-dependent memory in rats. Behav Brain Res **155**:77-84.

Gerges NZ, and Alkadhi KA (2004) Hypothyroidism impairs late LTP in CA1 region but not in dentate gyrus of the intact rat hippocampus: MAPK involvement. Hippocampus **14**:40-45.

Gerges NZ, Alzoubi KH, and Alkadhi KA (2005) Role of phosphorylated CaMKII and calcineurin in the differential effect of hypothyroidism on LTP of CA1 and dentate gyrus. Hippocampus **15**:480-490.

Gilabert-Juan J, Bueno-Fernandez C, Castillo-Gomez E, and Nacher J (2017) Reduced interneuronal dendritic arborization in CA1 but not in CA3 region of mice subjected to chronic mild stress. Brain Behav **7**:e00534. doi:10.1002/brb3.534.

Gilbert ME (2004) Alterations in synaptic transmission and plasticity in area CA1 of adult hippocampus following developmental hypothyroidism." Brain Res Dev Brain Res **148**: 11-18.

Gilbert, M. E. and C. Paczkowski (2003) Propylthiouracil (PTU)-induced hypothyroidism in the developing rat impairs synaptic transmission and plasticity in the dentate gyrus of the adult hippocampus. Brain Res Dev Brain Res **145**: 19-29.

Gold PE, Delanoy RL, and Merrin J (1984) Modulation of long-term potentiation by peripherally administered amphetamine and epinephrine. Brain Res **305**:103-107.

Green KN, Billings LM, Roozendaal B, McGaugh JL, and LaFerla FM (2006) Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer's disease. J Neurosci **26**:9047-9056.

Grilli M, Chiu JJ, and Lenardo MJ (1993) NF-kappa B and Rel: participants in a multiform transcriptional regulatory system. Int Rev Cytol **143**:1-62.

Grobe JE, Perkins KA, Goettler-Good J, and Wilson A (1998) Importance of environmental distractors in the effects of nicotine on short-term memory. Exp Clin Psychopharmacol **6**:209-216.

Haggerty, J J, Jr., Garbutt JC, Evans DL, Golden RN, Pedersen C, Simon JS, and Nemeroff CB (1990) Subclinical hypothyroidism: a review of neuropsychiatric aspects. Int J Psychiatry Med **20**:193-208.

Helfand, M and Crapo LM (1990) Screening for thyroid disease." Ann Intern Med **112**: 840-849.

Hillier V, and Salib E (1997) A case-control study of smoking and Alzheimer's disease. Int J Geriatr Psychiatry **12**:295-300.

Holscher C (1999) Stress impairs performance in spatial water maze learning tasks. Behav Brain Res **100**:225-235.

Hueston, WJ (2001) Treatment of hypothyroidism. Am Fam Physician **64**: 1717-1724.

Itoh A, Akaike T, Sokabe M, Nitta A, Iida R, Olariu A, Yamada K, Nabeshima T (1999) Impairments of long-term potentiation in hippocampal slices of beta-amyloid-infused rats. Eur J Pharmacol **382**:167-175.

Ivanco TL, and Racine RJ (2000) Long-term potentiation in the reciprocal corticohippocampal and corticocortical pathways in the chronically implanted, freely moving rat. Hippocampus **10**:143-152.

Jamal M, Van der Does W, Elzinga BM, Molendijk ML, and Penninx BW (2015) Association between smoking nicotine dependence and BDNF Val66Met polymorphism with BDNF concentrations in serum. Nicotine Tobac Res **17**:323–329

Joels M (2006) Corticosteroid effects in the brain: U-shape it. Trends Pharmacol Sci **27**:244-250.

Kasa P, Rakonczay Z, and Gulya K (1997) The cholinergic system in Alzheimer's disease. Prog Neurobiol **52**:511-535.

Kenney JW, and Gould TJ (2008) Modulation of hippocampus-dependent learning and synaptic plasticity by nicotine. Mol Neurobiol **38**:101-121.

Kirschbaum C, Wolf OT, May M, Wippich W, and Hellhammer DH (1996) Stress- and treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. Life Sci **58**:1475-1483.

Kroker KS, Moreth J, Kussmaul L, Rast G, and Rosenbrock H (2013) Restoring long-term potentiation impaired by amyloid-beta oligomers: comparison of an acetylcholinesterase inhibitor and selective neuronal nicotinic receptor agonists. Brain Res Bull **96**:28-38.

Kulstad JJ, McMillan PJ, Leverenz JB, Cook DG, Green PS, Peskind ER, Wilkinson CW, Farris W, Mehta PD, and Craft S (2005) Effects of chronic glucocorticoid administration on insulin-degrading enzyme and amyloid-beta peptide in the aged macaque. J Neuropathol Exp Neurol **64**:139-146.

Lahiri DK, Utsuki T, Chen D, Farlow MR, Shoaib M, Ingram DK, and Greig NH (2002) Nicotine reduces the secretion of Alzheimer's beta-amyloid precursor protein containing beta-amyloid peptide in the rat without altering synaptic proteins. Ann N Y Acad Sci **965**:364-372.

Lee PN (1994) Smoking and Alzheimer's disease: a review of the epidemiological evidence. Neuroepidemiology **13**:131-144.

Leentjens, AF, and Kappers EJ (1995) Persistent cognitive defects after corrected hypothyroidism. Psychopathology **28**:235-237.

Leist, M. and Nicotera, P (1998) Apoptosis, excitotoxicity, and neuropathology. Exp Cell Res **239**:183-201.

Levin ED, Bradley A, Addy N, and Sigurani N (2002) Hippocampal alpha 7 and alpha 4 beta 2 nicotinic receptors and working memory. Neuroscience **109**:757-765.

Levin ED, Briggs SJ, Christopher NC, and Rose JE (1992) Persistence of chronic nicotine-induced cognitive facilitation. Behav Neural Biol **58**:152-158.

Levin ED, Briggs SJ, Christopher NC, and Rose JE (1993a) Chronic nicotinic stimulation and blockade effects on working memory. Behav Pharmacol **4**:179-182.

Levin ED, Christopher NC, Briggs SJ, and Rose JE (1993b) Chronic nicotine reverses working memory deficits caused by lesions of the fimbria or medial basalocortical projection. Brain Res Cogn Brain Res **1**:137-143.

Levin ED, Castonguay M, and Ellison GD (1987) Effects of the nicotinic receptor blocker mecamylamine on radial-arm maze performance in rats. Behav Neural Biol **48**:206-212.

Levin ED, Christopher NC, and Briggs SJ (1997) Chronic nicotinic agonist and antagonist effects on T-maze alternation. Physiol Behav **61**:863-866.

Levin ED, Conners CK, Silva D, Hinton SC, Meck WH, March J, and Rose JE (1998) Transdermal nicotine effects on attention. Psychopharmacology (Berl) **140**:135-141.

Levin ED, Wilson W, Rose JE, and McEvoy J (1996a) Nicotine-haloperidol interactions and cognitive performance in schizophrenics. Neuropsychopharmacology **15**:429-436.

Levin ED, Conners CK, Sparrow E, Hinton SC, Erhardt D, Meck WH, Rose JE, and March J (1996b) Nicotine effects on adults with attention-deficit/hyperactivity disorder. Psychopharmacology (Berl) **123**:55-63.

Levin ED, Lee C, Rose JE, Reyes A, Ellison G, Jarvik M, and Gritz E (1990) Chronic nicotine and withdrawal effects on radial-arm maze performance in rats. Behav Neural Biol **53**:269-276.

Levin ED, and Rezvani AH (2000) Development of nicotinic drug therapy for cognitive disorders. Eur J Pharmacol **393**:141-146.

Levin ED, and Rose JE (1990) Anticholinergic sensitivity following chronic nicotine administration as measured by radial-arm maze performance in rats. Behav Pharmacol **1**:511-520.

Levin ED, and Simon BB (1998) Nicotinic acetylcholine involvement in cognitive function in animals. Psychopharmacology (Berl) **138**:217-230.

Levin ED, and Torry D (1996) Acute and chronic nicotine effects on working memory in aged rats. Psychopharmacology (Berl) **123**:88-97.

Lupien SJ, Gaudreau S, Tchiteya BM, Maheu F, Sharma S, Nair NP, Hauger RL, McEwen BS, and Meaney MJ (1997) Stress-induced declarative memory impairment in healthy elderly subjects: relationship to cortisol reactivity. J Clin Endocrinol Metab **82**:2070-2075.

Machaalani R, and Chen H (2018) Brain derived neurotrophic factor (BDNF), its tyrosine kinase receptor B (TrkB) and nicotine. Neurotoxicology **65**:186-195.

Magarinos AM, and McEwen BS (1995) Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: involvement of glucocorticoid secretion and excitatory amino acid receptors. Neuroscience **69**:89-98.

Maggio R, Riva M, Vaglini F, Fornai F, Molteni R, Armogida M, Racagni G, and Corsini GU (1998) Nicotine prevents experimental parkinsonism in rodents and induces striatal increase of neurotrophic factors. J Neurochem **71**:2439-2446.

Maggio R, Riva M, Vaglini F, Fornai F, Racagni G, and Corsini GU (1997) Striatal increase of neurotrophic factors as a mechanism of nicotine protection in experimental parkinsonism. J Neural Transm **104**:1113-1123.

Matsuyama S, Matsumoto A, Enomoto T, and Nishizaki T (2000) Activation of nicotinic acetylcholine receptors induces long-term potentiation in vivo in the intact mouse dentate gyrus. Eur J Neurosci **12**:3741-3747.

Mattson MP (2004) Pathways towards and away from Alzheimer's disease. Nature **430**:631-639.

Maurice T, Lockhart BP, and Privat A (1996) Amnesia induced in mice by centrally administered beta-amyloid peptides involves cholinergic dysfunction. Brain Res **706**:181-193.

McCarley, RW (2007) Neurobiology of REM and NREM sleep. Sleep Med **8**:302-330.

McEwen BS (1999) Stress and hippocampal plasticity. Annu Rev Neurosci **22**:105-122.

McEwen BS (2000) The neurobiology of stress: from serendipity to clinical relevance. Brain Res **886**:172-189.

McEwen BS, and Sapolsky RM (1995) Stress and cognitive function. Curr Opin Neurobiol **5**:205-216.

McEwen, B. S (1997) Possible mechanisms for atrophy of the human hippocampus. Mol Psychiatry **2**:255-262.

McNaughton BL, and Foster TC (1990) The cellular basis of memory. Science **249**:1487.

Meldrum B. and Garthwaite J (1990) Excitatory amino acid neurotoxicity and neurodegenerative disease. Trends Pharmacol Sci **11**:379-387.

Mesulam MM (1996) The systems-level organization of cholinergic innervation in the human cerebral cortex and its alterations in Alzheimer's disease. Prog Brain Res **109**:285-297.

Moghaddam B, Bolinao ML, Stein-Behrens B. and Sapolsky, R (1994) Glucocorticoids mediate the stress-induced extracellular accumulation of glutamate. *Brain Res.*; **655**:251-4.

Morens DM, Grandinetti A, Reed D, White LR and Ross GW (1995) Cigarette smoking and protection from Parkinson's disease: false association or etiologic clue? Neurology **45**:1041-1051.

Mugnaini M, Tessari M, Tarter G, Merlo Pich E, Chiamulera C, and Bunnemann B (2002) Upregulation of [3H]methyllycaconitine binding sites following continuous infusion of nicotine, without changes of alpha7 or alpha6 subunit mRNA: an autoradiography and in situ hybridization study in rat brain. Eur J Neurosci **16**:1633-1646.

Nagele RG, D'Andrea MR, Anderson WJ, and Wang HY (2002) Intracellular accumulation of beta-amyloid(1-42) in neurons is facilitated by the alpha 7 nicotinic acetylcholine receptor in Alzheimer's disease. Neuroscience **110**:199-211.

Nayak AS, Moore CI, and Browning MD (1996) Ca2+/calmodulin-dependent protein kinase II phosphorylation of the presynaptic protein synapsin I is persistently increased during long-term potentiation. Proc Natl Acad Sci U S A **93**:15451-15456.

Neves CDC, Lacerda ACR, Lima LP, Lage VKS, Balthazar CH, Leite HR, and Mendonça VA (2017) Different levels of brain-derived neurotrophic factor and cortisol in healthy heavy smokers. Braz J Med Biol Res **50**: e6424

Newhouse PA, Potter A, Kelton M, and Corwin J (2001) Nicotinic treatment of Alzheimer's disease. Biol Psychiatry **49**:268-278.

Newhouse PA, Potter A, and Levin ED (1997) Nicotinic system involvement in Alzheimer's and Parkinson's diseases. Implications for therapeutics. Drugs Aging **11**:206-228.

Newhouse PA, Sunderland T, Tariot PN, Blumhardt CL, Weingartner H, Mellow A, and Murphy DL (1988) Intravenous nicotine in Alzheimer's disease: a pilot study. Psychopharmacology (Berl) **95**:171-175.

Niemi WD, Slivinski K, Audi J, Rej R, and Carpenter DO (1996) Propylthiouracil treatment reduces long-term potentiation in area CA1 of neonatal rat hippocampus. Neurosci Lett **210**:127-129.

Osterweil D, Syndulko K, Cohen SN, Pettler-Jennings PD, Hershman JM, Cummings JL, Tourtellotte WW, and Solomon DH (1992) Cognitive function in non-demented older adults with hypothyroidism. J Am Geriatr Soc **40**:325-335.

Park S, Knopick C, McGurk S, and Meltzer HY (2000) Nicotine impairs spatial working memory while leaving spatial attention intact. Neuropsychopharmacology **22**:200-209.

Parker SL, Fu Y, McAllen K, Luo J, McIntosh JM, Lindstrom JM, and Sharp BM (2004) Up-regulation of brain nicotinic acetylcholine receptors in the rat during long-term self-administration of nicotine: disproportionate increase of the alpha6 subunit. Mol Pharmacol **65**:611-622.

Parpura-Gill A, Beitz D, and Uemura E (1997) The inhibitory effects of beta-amyloid on glutamate and glucose uptakes by cultured astrocytes. Brain Res **754**:65-71.

Parrott AC and Winder G (1989) Nicotine chewing gum (2 mg, 4 mg) and cigarette smoking: comparative effects upon vigilance and heart rate. Psychopharmacology (Berl) **97:**257-261.

Paterson D and Nordberg A (2000) Neuronal nicotinic receptors in the human brain. Prog Neurobiol **61**:75-111.

Pauly JR, and Collins AC (1993) An autoradiographic analysis of alterations in nicotinic cholinergic receptors following 1 week of corticosterone supplementation. Neuroendocrinology **57**:262-271.

Pavlides C and McEwen BS (1999) Effects of mineralocorticoid and glucocorticoid receptors on long-term potentiation in the CA3 hippocampal field. Brain Res **851**:204-214.

Pavlides C, Ogawa S, Kimura A, and McEwen BS (1996) Role of adrenal steroid mineralocorticoid and glucocorticoid receptors in long-term potentiation in the CA1 field of hippocampal slices. Brain Res **738**:229-235.

Pavlides C, Watanabe Y, and McEwen BS (1993) Effects of glucocorticoids on hippocampal long-term potentiation. Hippocampus **3**:183-192.

Pedersen WA, McMillan PJ, Kulstad JJ, Leverenz JB, Craft S, and Haynatzki GR (2006) Rosiglitazone attenuates learning and memory deficits in Tg2576 Alzheimer mice. Exp Neurol **199**:265-273.

Perry E, Martin-Ruiz C, Lee M, Griffiths M, Johnson M, Piggott M, Haroutunian V, Buxbaum JD, Nasland J, Davis K, Gotti C, Clementi F, Tzartos S, Cohen O, Soreq H, Jaros E, Perry R, Ballard C, McKeith I, and Court J (2000) Nicotinic receptor subtypes in human brain ageing, Alzheimer and Lewy body diseases. Eur J Pharmacol **393**:215-222.

Pettit DL, Shao Z, and Yakel JL (2001) beta-Amyloid(1-42) peptide directly modulates nicotinic receptors in the rat hippocampal slice. J Neurosci **21**:RC120.

Porterfield SP (1994) Vulnerability of the developing brain to thyroid abnormalities: environmental insults to the thyroid system. Environ Health Perspect **102** Suppl 2:125-130.

Porterfield SP, and Hendrich CE (1991) The thyroidectomized pregnant rat--an animal model to study fetal effects of maternal hypothyroidism. Adv Exp Med Biol **299**:107-132.

Rezvani AH, Bushnell PJ, and Levin ED (2002) Effects of nicotine and mecamylamine on choice accuracy in an operant visual signal detection task in female rats. Psychopharmacology (Berl) **164**:369-375.

Ridley DL, Rogers A, and Wonnacott S (2001) Differential effects of chronic drug treatment on alpha3* and alpha7 nicotinic receptor binding sites, in hippocampal neurones and SH-SY5Y cells. Br J Pharmacol **133**:1286-1295.

Rovet JF (1999) Congenital hypothyroidism: long-term outcome. Thyroid **9**:741-748.

Sahakian B, Jones G, Levy R, Gray J, and Warburton D (1989) The effects of nicotine on attention, information processing, and short-term memory in patients with dementia of the Alzheimer type. Br J Psychiatry **154**:797-800.

Sakimura K, Kutsuwada T, Ito I, Manabe T, Takayama C, Kushiya E, Yagi T, Aizawa S, Inoue Y, Sugiyama H, et al (1995) Reduced hippocampal LTP and spatial learning in mice lacking NMDA receptor epsilon 1 subunit. Nature **373**:151-155.

Sapolsky RM (2000) The possibility of neurotoxicity in the hippocampus in major depression: a primer on neuron death. Biol Psychiatry **48**:755-765.

Sapolsky RM, Uno H, Rebert CS, and Finch CE (1990) Hippocampal damage associated with prolonged glucocorticoid exposure in primates. J Neurosci **10**:2897-2902.

Sapolsky RM (1993) Potential behavioral modification of glucocorticoid damage to the hippocampus. Behav Brain Res **57**:175-182.

Schoenfeld TJ, McCausland HC, Morris HD, Padmanaban V, and Cameron HA (2017) Stress and Loss of Adult Neurogenesis Differentially Reduce Hippocampal Volume. Biol Psychiatry **82**:914-923.

Seguela P, Wadiche J, Dineley-Miller K, Dani JA, and Patrick JW (1993) Molecular cloning, functional properties, and distribution of rat brain alpha 7: a nicotinic cation channel highly permeable to calcium. J Neurosci **13**:596-604.

Semba K, and Fibiger HC (1989) Organization of central cholinergic systems. Prog Brain Res **79**:37-63.

Shors TJ, Foy MR, Levine S, and Thompson RF (1990) Unpredictable and uncontrollable stress impairs neuronal plasticity in the rat hippocampus. Brain Res Bull **24**:663-667.

Shors TJ, and Thompson RF (1992) Acute stress impairs (or induces) synaptic long-term potentiation (LTP) but does not affect paired-pulse facilitation in the stratum radiatum of rat hippocampus. Synapse **11**:262-265.

Smith MA (1996) Hippocampal vulnerability to stress and aging: possible role of neurotrophic factors. Behav Brain Res **78**:25-36.

Snyder SW, Ladror US, Wade WS, Wang GT, Barrett LW, Matayoshi ED, Huffaker HJ, Krafft GA, and Holzman TF (1994) Amyloid-beta aggregation: selective inhibition of aggregation in mixtures of amyloid with different chain lengths. Biophys J **67**:1216-1228.

Socci DJ, Sanberg PR, and Arendash GW (1995) Nicotine enhances Morris water maze performance of young and aged rats. Neurobiol Aging **16**:857-860.

Sorenson CA, Raskin LA, and Suh Y (1991) The effects of prenatal nicotine on radial-arm maze performance in rats. Pharmacol Biochem Behav **40**:991-993.

Srivareerat M, Tran TT, Alzoubi KH, and Alkadhi KA (2009) Chronic psychosocial stress exacerbates impairment of cognition and long-term potentiation in beta-amyloid rat model of Alzheimer's disease. Biol Psychiatry **65**:918-926.

Srivareerat M, Tran TT, Salim S, Aleisa AM, and Alkadhi KA (2011) Chronic nicotine restores normal Aβ levels and prevents short-term memory and E-LTP impairment in Aβ rat model of Alzheimer's disease. Neurobiol Aging **32**:834-844.

Starkman MN, Giordani B, Gebarski SS, Berent S, Schork MA, and Schteingart DE (1999) Decrease in cortisol reverses human hippocampal atrophy following treatment of Cushing's disease. Biol Psychiatry **46**:1595-1602.

Sui L, Anderson WL, and Gilbert ME (2005) Impairment in short-term but enhanced long-term synaptic potentiation and ERK activation in adult hippocampal area CA1 following developmental thyroid hormone insufficiency. Toxicol Sci **85**:647-656

Suriyaprom K, Tungtrongchitr R, Thawnashom K, and Pimainog Y (2013) BDNF Val66Met polymorphism and serum concentrations of BDNF with smoking in Thai males. Genet Mol Res **12:**4925–4933

Sutherland RJ, McDonald RJ, Hill CR, and Rudy JW (1989) Damage to the hippocampal formation in rats selectively impairs the ability to learn cue relationships. Behav Neural Biol **52**:331-356.

Sze CI, Troncoso JC, Kawas C, Mouton P, Price DL, and Martin LJ (1997) Loss of the presynaptic vesicle protein synaptophysin in hippocampus correlates with cognitive decline in Alzheimer disease. J Neuropathol Exp Neurol **56**:933-944.

Takita M, and Muramatsu I (1995) Alteration of brain nicotinic receptors induced by immobilization stress and nicotine in rats. Brain Res **681**:190-192.

Takita M, Taniguchi T, Zhu J, Piao HL, Tsai TY, and Muramatsu I (1999) Effects of chronic treatment with (+)-nicotine on the stress-induced hypertension and downregulation of central nicotinic receptors in rats: comparative study with (-)-nicotine. Gen Pharmacol **33**:29-33.

Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, and Katzman R (1991) Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol **30**:572-580.

Tran TT, Srivareerat M, and Alkadhi KA (2010) Chronic psychosocial stress triggers cognitive impairment in a novel at-risk model of Alzheimer's disease. Neurobiol Dis **37**:756-763.

Tran TT, Srivareerat M, Alhaider IA, and Alkadhi KA (2011a) Chronic psychosocial stress enhances long-term depression in a subthreshold amyloid-beta rat model of Alzheimer's disease. J Neurochem **119**:408-416.

Tran TT, Srivareerat M, and Alkadhi KA (2011b) Chronic psychosocial stress accelerates impairment of long-term memory and late-phase long-term potentiation in an at-risk model of Alzheimer's disease. Hippocampus **21**:724-732.

Ulrich J, Johannson-Locher G, Seiler WO, and Stahelin HB (1997) Does smoking protect from Alzheimer's disease? Alzheimer-type changes in 301 unselected brains from patients with known smoking history. Acta Neuropathol **94**:450-454.

Utsuki T, Shoaib M, Holloway HW, Ingram DK, Wallace WC, Haroutunian V, Sambamurti K, Lahiri DK, and Greig NH (2002) Nicotine lowers the secretion of the Alzheimer's amyloid

beta-protein precursor that contains amyloid beta-peptide in rat. J Alzheimers' disease Dis **4**:405-415.

van Duijn CM and Hofman A (1991) Relation between nicotine intake and Alzheimer's disease. The BMJ **302**:1491-1494.

Vara H, Munoz-Cuevas J, and Colino A (2003) Age-dependent alterations of long-term synaptic plasticity in thyroid-deficient rats. Hippocampus **13**: 816-825.

Vereker E, O'Donnell E, Lynch A, Kelly A, Nolan Y, and Lynch MA (2001) Evidence that interleukin-1beta and reactive oxygen species production play a pivotal role in stress-induced impairment of LTP in the rat dentate gyrus. Eur J Neurosci **14**:1809-1819.

Wada E, Wada K, Boulter J, Deneris E, Heinemann S, Patrick J, and Swanson LW (1989) Distribution of alpha 2, alpha 3, alpha 4, and beta 2 neuronal nicotinic receptor subunit mRNAs in the central nervous system: a hybridization histochemical study in the rat. J Comp Neurol **284**:314-335.

Wang HY, Lee DH, Davis CB, and Shank RP (2000a) Amyloid peptide Abeta(1-42) binds selectively and with picomolar affinity to alpha7 nicotinic acetylcholine receptors. J Neurochem **75**:1155-1161.

Wang HY, Lee DH, D'Andrea MR, Peterson PA, Shank RP, and Reitz AB (2000b) beta-Amyloid(1-42) binds to alpha7 nicotinic acetylcholine receptor with high affinity. Implications for Alzheimer's disease pathology. J Biol Chem **275**:5626-5632.

Wang HL, Chen XT, Luo L, Lou ZY, Wang S, Chen JT, Wang M, Sun LG, and Ruan DY (2006) Reparatory effects of nicotine on NMDA receptor-mediated synaptic plasticity in the hippocampal CA1 region of chronically lead-exposed rats. Eur J Neurosci **23**:1111-1119.

Watanabe Y, Gould E, Cameron HA, Daniels DC, and McEwen BS (1992a) Phenytoin prevents stress- and corticosterone-induced atrophy of CA3 pyramidal neurons. Hippocampus **2**:431-435.

Watanabe Y, Gould E, and McEwen BS (1992b) Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. Brain Res **588**:341-345.

Webster MJ, Weickert CS, Herman MM, and Kleinman JE (2002) BDNF mRNA expression during postnatal development maturation and aging of the human prefrontal cortex. Brain Res Dev Brain Res **139**:139–150

Wesnes K, and Warburton DM (1984) Effects of scopolamine and nicotine on human rapid information processing performance. Psychopharmacology (Berl) **82**:147-150.

White HK, and Levin ED (1999) Four-week nicotine skin patch treatment effects on cognitive performance in Alzheimer's disease. Psychopharmacology (Berl) **143**:158-165.

White HK, and Levin ED (2004) Chronic transdermal nicotine patch treatment effects on cognitive performance in age-associated memory impairment. Psychopharmacology (Berl) **171**:465-471.

Whitehouse PJ, Price DL, Struble RG, Clark AW, Coyle JT, and Delon MR (1982) Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. Science **215**:1237-1239.

Wilson AL, Langley LK, Monley J, Bauer T, Rottunda S, McFalls E, Kovera C, and McCarten JR (1995) Nicotine patches in Alzheimer's disease: pilot study on learning, memory, and safety. Pharmacol Biochem Behav **51**:509-514.

Wilson RS, Barnes LL, Bennett DA, Li Y, Bienias JL, Mendes de Leon CF, and Evans DA (2005) Proneness to psychological distress and risk of Alzheimer disease in a biracial community. Neurology **64**:380-382.

Wilson RS, Evans DA, Bienias JL, Mendes de Leon CF, Schneider JA, and Bennett DA (2003) Proneness to psychological distress is associated with risk of Alzheimer's disease. Neurology **61**:1479-1485.

Witter MP, Van Hoesen GW, and Amaral DG (1989) Topographical organization of the entorhinal projection to the dentate gyrus of the monkey. J Neurosci **9**:216-228.

Woolf NJ (1991) Cholinergic systems in mammalian brain and spinal cord. Prog Neurobiol **37**:475-524.

Xu W, Orr-Urtreger A, Nigro F, Gelber S, Sutcliffe CB, Armstrong D, Patrick JW, Role LW, Beaudet AL, and De Biasi M (1999) Multiorgan autonomic dysfunction in mice lacking the beta2 and the beta4 subunits of neuronal nicotinic acetylcholine receptors. J Neurosci **19**:9298-9305.

Xu KL, Liu XQ, Yao YL, Ye MR, Han YG, Zhang T, Chen G, and Lei M (2018) Effect of dexmedetomidine on rats with convulsive status epilepticus and association with activation of cholinergic anti-inflammatory pathway. Biochem Biophys Res Commun **495**:421-426

Yamazaki Y, and Sumikawa K (2017) Nicotine-induced neuroplasticity counteracts the effect of schizophrenia-linked neuregulin 1 signaling on NMDAR function in the rat hippocampus. Neuropharmacology **113**(Pt A):386-395.

Yehuda R (2001) Biology of posttraumatic stress disorder. J Clin Psychiatry **62** Suppl 17:41-46.

Ying SW, Futter M, Rosenblum K, Webber MJ, Hunt SP, Bliss TV, and Bramham CR (2002) Brain-derived neurotrophic factor induces long-term potentiation in intact adult hippocampus: requirement for ERK activation coupled to CREB and upregulation ofArc synthesis. J Neurosci **22**:1532-1540.

Zagaar M, Alhaider I, Dao A, Levine A, Alkarawi A, Alzubaidy M, and Alkadhi K (2012) The beneficial effects of regular exercise on cognition in REM sleep deprivation: behavioral, electrophysiological and molecular evidence. Neurobiol Dis **45**:1153-1162.

Zagaar M, Dao A, Levine A, Alhaider I, and Alkadhi K (2013a) Regular exercise prevents sleep deprivation associated impairment of long-term memory and synaptic plasticity in the CA1 area of the hippocampus. Sleep **36**:751-761.

Zagaar M, Dao A, Alhaider I, and Alkadhi K (2013b) Regular treadmill exercise prevents sleep deprivation-induced disruption of synaptic plasticity and associated signaling cascade in the dentate gyrus. Mol Cell Neurosci **56**:375-383.

Zagaar MA, Dao AT, Alhaider IA, and Alkadhi KA (2016) Prevention by Regular Exercise of Acute Sleep Deprivation-Induced Impairment of Late Phase LTP and Related Signaling Molecules in the Dentate Gyrus. Mol Neurobiol **53**:2900-2910.

Ziedonis D, Hitsman B, Beckham JC, Zvolensky M, Adler LE, Audrain-McGovern J, Breslau N, Brown RA, George TP, Williams J, Calhoun PS, and Riley WT (2008) Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. Nicotine Tob Res **10**:1691-1715.

Zhang XY, Xiu MH, Chen DC, Yang FD, Wu GY, Lu L, Kosten TA, and Kosten TR (2010) Nicotine dependence and serum BDNF levels in male patients with schizophrenia. Psychopharmacology **212**:301–307

Zhou J, Zhang F, and Zhang Y (2000) Corticosterone inhibits generation of long-term potentiation in rat hippocampal slice: involvement of brain-derived neurotrophic factor. Brain Res **885**:182-191.

Zhou X, Nai Q, Chen M, Dittus JD, Howard MJ, and Margiotta JF (2004) Brain-derived neurotrophic factor and trkB signaling in parasympathetic neurons: relevance to regulating a7-containing nicotinic receptors and synaptic function. J Neurosci **24:**4340–4350

**Footnotes:**

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## Figures Legends

**Figure 1**: The protective effect of nicotine on synaptic plasticity in area CA1 of Aβ rat model of Alzheimer's disease with chronic stress. (A) Chronic nicotine treatment prevents impairment of early phase LTP (E-LTP) caused by i.c.v. infusion of Aβ in Aβ rat model of Alzheimer's disease. E-LTP of the CA1 region was evoked by HFS (applied at time 0) of the Schaffer collateral/commissural pathway of urethane-anesthetized rats. (B) Nicotine prevents stress-exacerbated impairment of hippocampal late-phase long-term potentiation (L-LTP) in area CA1 of Aβ rats. L-LTP was induced by multiple high frequency stimulation (MHFS) applied at time 0. Both E-LTP and L-LTP were measured as increases in slope of field excitatory postsynaptic potential (fEPSP). Each point is the mean ± S.E.M. from 5-7 rats. * Indicates points are significantly different from control group and # indicates points are significantly different from all other groups; ($p<0.05$). Modified from (Srivareerat et al., 2011; Alkadhi et al., 2011).

**Figure 2:** Chronic nicotine treatment reverses hypothyroidism-induced impairment of synaptic plasticity in area CA1 of rat hippocampus. (A) E-LTP was measured as an increase in f-EPSP slope. The fEPSP slope in all points after HFS was significantly ($p<0.05$) lower in the hypothyroid group compared with the other groups. E-LTP magnitude, in nicotine-treated hypothyroid rats, was comparable with that in control or nicotine-treated rats. Similar results were obtained with L-LTP of area CA1(B). Each point in each group is the mean ± SEM from 6 to 7 rats. Methods details are as in Figure 1. Adapted from (Alzoubi et al., 2006 a, b). * Indicates points are significantly different from all other groups .

**Figure 3**: Nicotine treatment (24 h) prevents sleep deprivation (SD 24 hour)-induced impairment of spatial learning and short-term memory (30-min) (A) as tested in the radial arm water maze. The RAWM is a black circular pool filled with water at room-temperature containing six swim paths from one open central area. The experiments are carried out in a dimly lit room with visual cues placed on the surrounding walls. Each rat is randomly assigned a goal arm, which contains a hidden black platform (2 cm below the water level) near the end of the arm. The rats are randomly released at an arm different from the goal arm where they would swim and locate the platform, which is submerged about 1 cm under the water. The rats were allowed a maximum time of 1 minute for each learning trial or memory tests. An error was counted when the rat entered more than halfway into an arm other than the goal arm. The number of errors ranged from 1 to a maximum of 7, as the rat could only swim into 7 arms within 1 minute. If the rat failed to locate the platform within 1 minute, the rat was manually guided to the platform and is scored with 7 errors. Upon reaching the platform, the rat was allowed 15 seconds sitting time on the platform before the next trial began. The effect of SD on short-term memory is also depicted in (B). Note impaired learning by SD in the second half of the trials. Nicotine administration (SD+Nic) prevents effects of SD on learning and memory. Data are presented as mean ± SEM (N= 9–11 rats). * Indicates significant difference from control, Nic and SD/Nic group. (from Aleisa et al., 2011a)

**Figure 4**: E-LTP of area CA1 was absent in rats sleep deprived for 24h (A) and 48h (B). Nicotine treatment completely prevented sleep deprivation-induced blockade of E-LTP. Each

point is the mean± SEM from four to seven rats. * Indicates points are significantly different from all other groups . Methods details are as in Figure 1. (Adapted from Aleisa et al., 2011).

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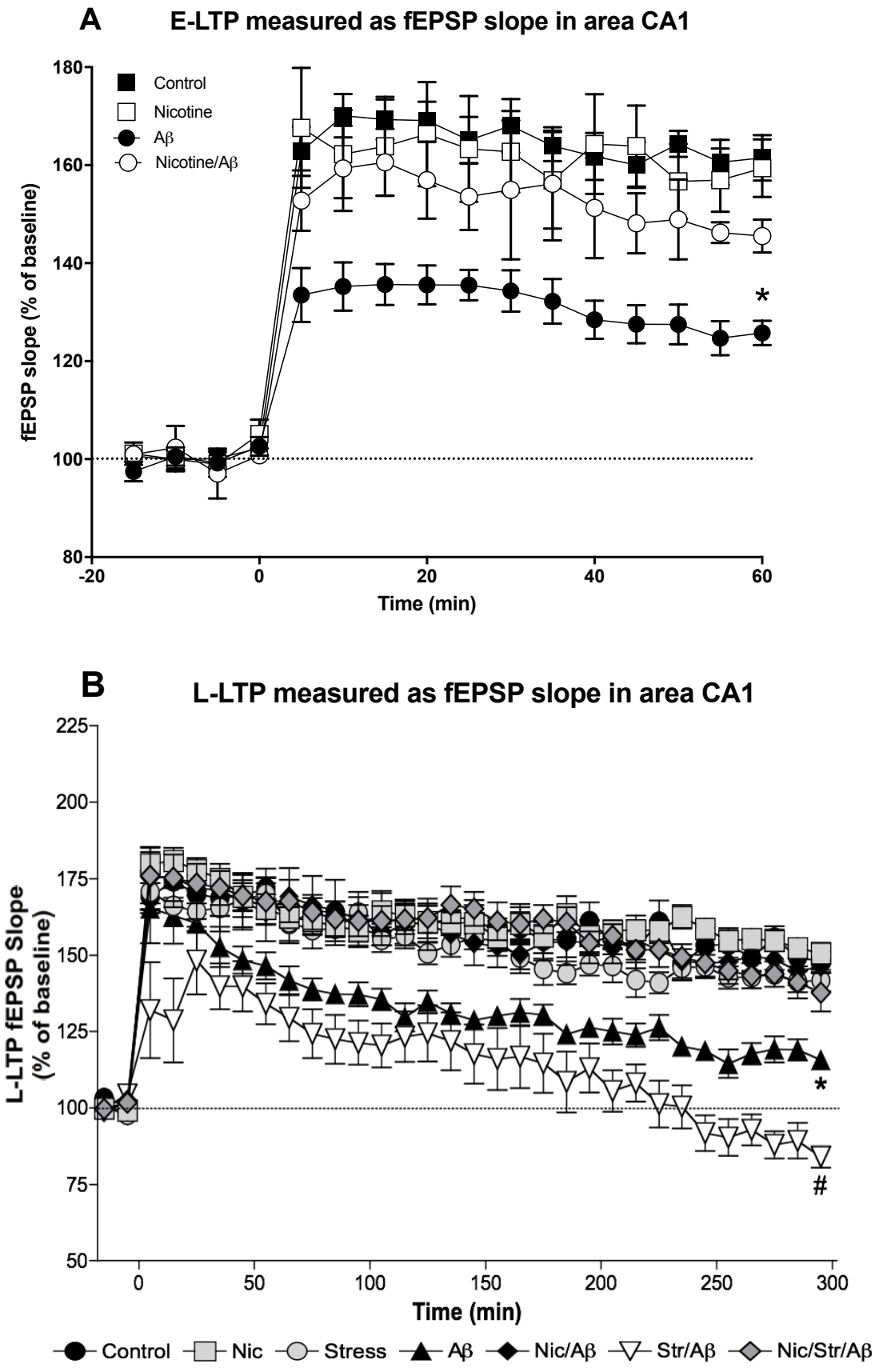

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Fig 2

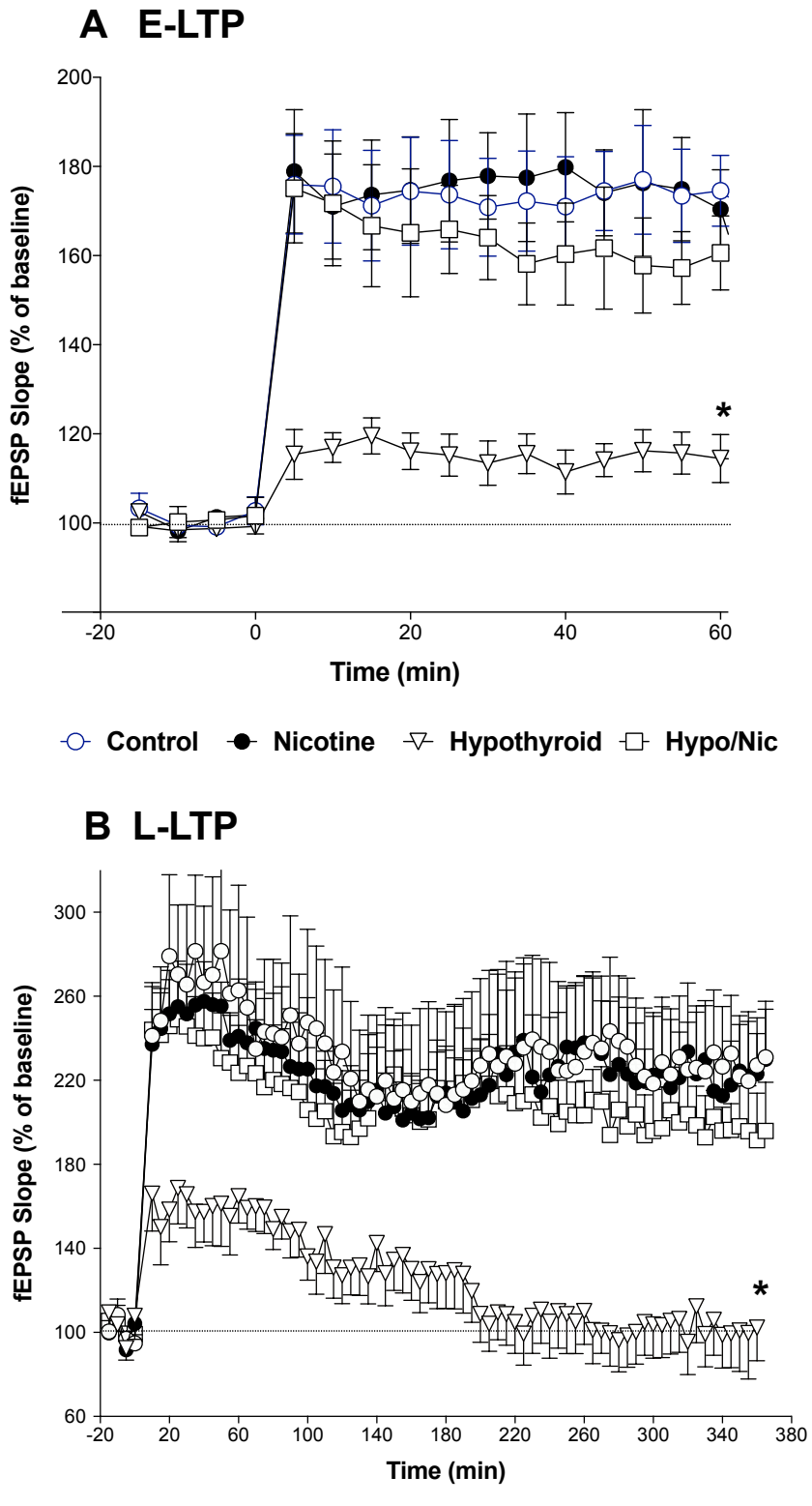

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Fig 3

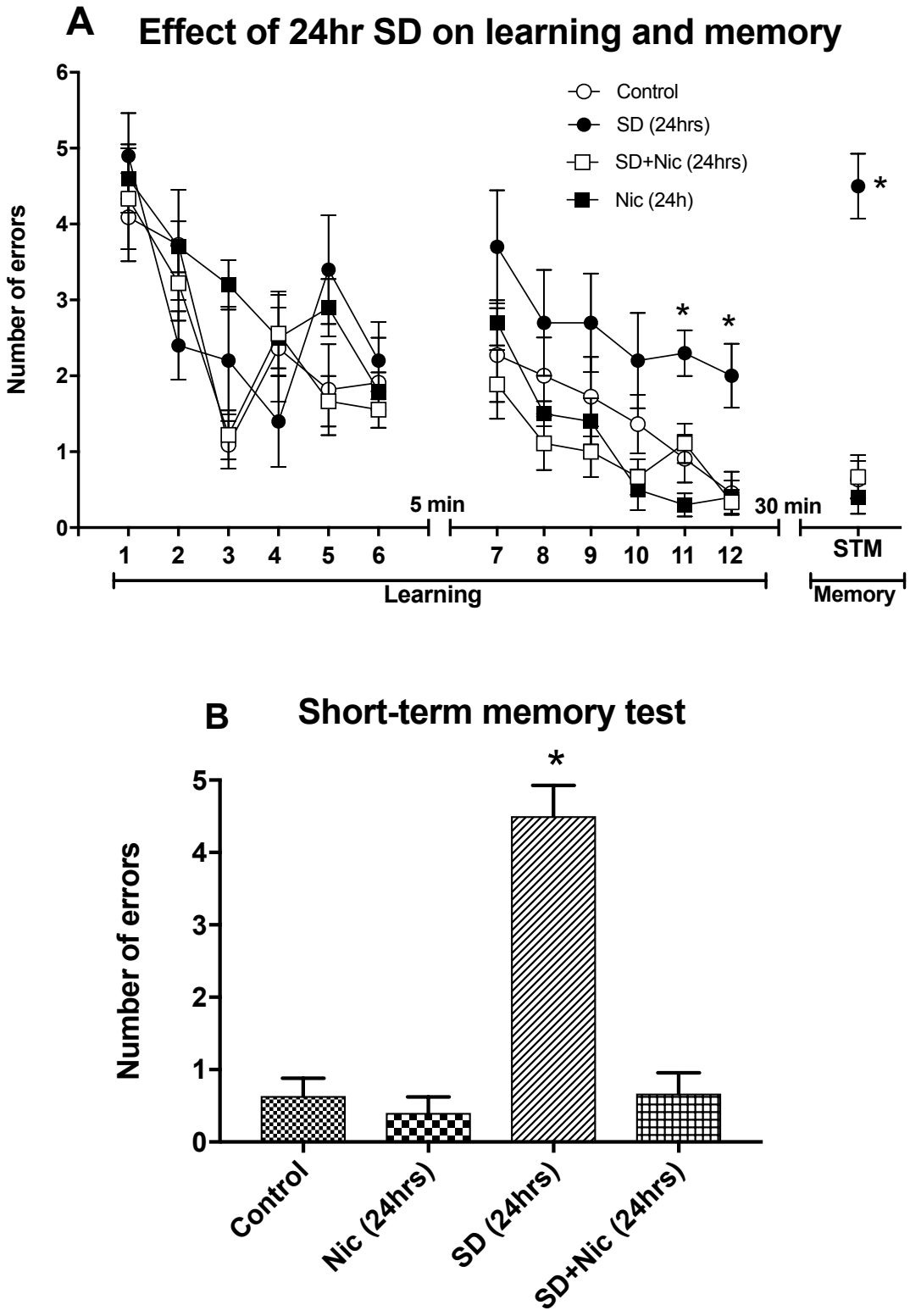

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Fig 4