Minireviews

Neuroprotective Effects of Nicotine on Hippocampal Long-Term Potentiation in Brain Disorders

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Received January 13, 2018; accepted May 23, 2018

ABSTRACT

Long-term potentiation (LTP) is commonly considered 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, related to short-term memory; and late-phase LTP, related to long-term memory. These two forms can be severely reduced in a variety of conditions 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 the cellular correlate of learning and memory. Most 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 both 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 trisynaptic 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 pathway. These use-related changes are known as synaptic plasticity, of which LTP is a prime example.

The LTP of the DG area is remarkably resistant to insults compared with those of other areas of the hippocampus. This protected status perhaps is due to the DG area being 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 the 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., 2003, 2005); however, in area CA1

This work was supported by University of Houston GEAR and SGP grants. https://doi.org/10.1124/jpet.118.247841.

ABBREVIATIONS: AD, Alzheimer disease; AMPAR, a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors; BDNF, brain-derived neurotrophic factor; CRE, cAMP-responsive element; CREB, cAMP-responsive element-binding protein; DG, dentate gyrus; E-LTP, early phase LTP; fEPSP, field excitatory postsynaptic potential; HFS, high frequency stimulation; L-LTP, late-phase LTP; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase; MHFS, multiple high frequency stimulation; MLA, methyllycaconitine; nAChR, nicotinic acetylcholine receptor; NMDA, N-methyl-D-aspartate; phosphorylated calcium-calmodulin-dependent protein kinase II pspike, population spike; NRG1, neuregulin 1; REM, rapid eye movement.
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 does require constitutive activation of p-CaMKII, which phosphorylates and enhances the conductivity of glutamate postsynaptic α3-3-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 stimulations (MHFSs) applied over a relatively long period. It is a protein synthesis–dependent phase, which requires activation of calcium-calmodulin-dependent protein kinase IV 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 necessary for synapse formation, neuronal survival, and long-term memory formation (Snyder et al., 1994).

Both forms of LTP can be measured by electrophysiologic techniques in the 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 the 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., 2006c; Tipps et al., 2014), aging (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 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., 1996b), attention deficit/hyperactivity disorder (Conners et al., 1996; Levin et al., 1996a, 1998), and Parkinson 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, 1992, 1993a, 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,c,d) 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 used.

The effect of nicotine on LTP has been widely studied in animal models of brain disorders (e.g., Kenney and Gould, 2008). Electrophysiologic 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 (Fuji et al., 1999, 2000b; Matsuyama et al., 2000; Fujii and Sumikawara, 2001), as well as in anesthetized rats (Aleisa et al., 2006a,c,d). The effects of nicotine on memory and LTP are prevented by mecamylamine, a nonselective 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, 1993a, 1997, 2002; Levin and Torry, 1996; Fujii et al., 1999; Matsuyama et al., 2000; Rezvani et al., 2002).

The nAChRs belong to a family of ligand gated ion channels that mediate fast synaptic transmission in the central nervous system (CNS). Structurally, nAChRs are composed 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 nAChR. The nAChRs can be of three major classifications based on their pharmacologic and physiologic properties: the heteropentameric nAChRs (α, β, δ, ε, τ), 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 Patrich, 1997). The hippocampus contains numerous nAChR subtypes; however, based on electrophysiologic 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; Séguela 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 (Riley et al., 2001; Muguinai 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., 2000a; 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 methylycarnitine (MLA) impairs memory and inhibits nicotine action on memory in the radial arm maze (Levin and Rezvani, 2000a; 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 GABA from these interneurons, hence indirectly promoting pyramidal cell excitability (Alkondon et al., 2000a,b). Consequently, LTP expression is facilitated by lowering its threshold of induction (Fujii et al., 1999, 2000b, 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. (1999) reported astroglisis and microgliosis with neocortical hypertrophy and hippocampal neuronal loss, resulting in impaired spatial learning.

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 Disease**

Alzheimer 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 presynaptic 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 pharmacologic data suggest that the high-affinity binding of the neurotoxic protein Aβ1-42 to α7- and α4β2-nAChRs has an important role in AD pathogenesis, including the formation of extracellular amyloid plaques and deterioration of cholinergic neurons (Wang et al., 2000a,b; Ikonomovic et al., 2009). It has been proposed that chronic stimulation of α7-nAChRs by Aβ1-42 protein accelerates disorder of ERK2-MAPK signaling pathway (Dineley et al., 2002), promotes internalization and intracellular accumulation of Aβ1-42 (Nagel et al., 2002), interferes with GABAergic signaling (Alkondon et al., 2000a), and/or further 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 epidemiologic 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 (1 mg/kg s.c. twice per day for 6 weeks before 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 a 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 (Itoh et al., 1999; Freir et al., 2001). For instance, Itoh and colleagues (1999) have reported that in slices from Aβ-infused rats, perfusion of 50 mM of nicotine for 10 minutes diminishes population spike amplitude in area CA1 of control rats. In similar studies, Freir et al. (2001) reported 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 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 resulting from excitotoxicity (Watanabe et al., 1992b; 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, 2004a; Aleisa et al., 2006d). 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., Gilabert-Juan et al., 2016; Schoenfeld et al., 2017) 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 laboratory, we have reported 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., 2006a,b), 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.
Interestingly, we show that acute bolus nicotine treatment fails to reverse the deleterious effects of stress on E-LTP (Aleisa et al., 2006b).

Co-occurrence of Alzheimer Disease and Chronic Stress

Chronic stress exacerbates the severity of cognitive decline in a variety of disorders (Vanitallie, 2002), including Cushing syndrome (Starkman et al., 1999), post-traumatic stress disorder (Yehuda, 2001), hypothyroidism (Gerges et al., 2001, 2004b), depression (McEwen, 1999), as well as AD (Srivareerat et al., 2009, 2011; Tran et al., 2010, 2011a,b). The physiologic consequences of stress depend on the intensity and duration of the stressor and 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, 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 neurototoxicity, and accelerated cognitive decline (Aisen et al., 2000; Pedersen et al., 2006; Srivareerat et al., 2009, 2011; Alkadhi et al., 2010, 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 Aβ 1-42 peptide that does
not affect normal cognition or synaptic plasticity (Tran et al., 2010, 2011a; Alkadhi and Tran, 2014). 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 but has no effects on the 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. Similarly, in area CA1, the L-LTP of the stressed/Aβ rat is more severely blocked with the combination treatment than that with Aβ treatment alone, and nicotine totally prevents the effect of the combination (Fig. 1B). 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 from 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 the elderly population (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 the skeletal system and CNS, resulting in severe mental retardation and 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 an 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 et al., 2006b). Synaptic plasticity impairment has also been reported in hypothyroidism. Hippocampal E-LTP is impaired during hypothyroidism at the neonatal stages (Niemi et al., 1996; Gilbert and Paczkowski, 2003), as well as adulthood (Gerges et al., 2001, 2005; Varà 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; Alzoubi and Alkadhi, 2007); 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; Alzoubi and Alkadhi, 2007). 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

![Fig. 2.](https://jpet.aspetjournals.org/doi/abs/10.1124/jpet.106.095070)

*Fig. 2. Chronic nicotine treatment reverses hypothyroidism-induced impairment of synaptic plasticity in area CA1 of the 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 to 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 ± S.E.M. from six to seven rats. Methods are as in Fig. 1. Adapted from Alzoubi et al. (2006 a,b).

*Points significantly different from all other groups.*
Sleep Deprivation

Sleep is characterized by cyclic occurrence of two major types of sleep: rapid eye movement (REM) and non-REM (slow wave or S). Studies have shown that during 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 the duration of REM sleep increasing and that of non-REM 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 a 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., 2010, 2011; Zagaar et al., 2012, 2013a,b). 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., 2010, 2011; Zagaar et al., 2012, 2013b).

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., 2010, 2011; Zagaar et al., 2012, 2013b) and DG areas (Marks and Wayner, 2005; Ishikawa et al., 2006; Alhaider et al., 2010; Zagaar et al., 2013a, 2016; Alhaider and Alkadhi, 2015). The negative effect of SD 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 brain-derived neurotrophic factor (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., 2010, 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., 2010; Zagaar et al., 2012, 2013a; 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 24 or 48 hours. Whereas 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., 2011b). Interestingly, even an acute dose of nicotine (1 mg/kg given three times during the 24-hour SD period) can prevent the effects of postlearning SD on long-term memory (Aleisa et al., 2011a). This effect 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 of 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 (s.c. injection of nicotine; 0.5–1 mg/kg, twice daily for 10–15 days) prevents impairment of LTP in NRG1β-treated rats (Yamazaki and Sumikawa, 2017).

Other Conditions

Various other conditions in which LTP is impaired and brain function is compromised have been 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., 2018). 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 (Fuji and Sumikawa, 2001). The age-related inhibition of LTP in the DG is also attenuated by nicotine (Curran and O'Connor, 2003). Environmental contaminants, such as the heavy metal lead, can cause marked cognitive impairments in children (Lidsky and Schneider, 2003; Meng et al., 2005) and experimental animals (Lasley and 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 and Gilbert, 1999; Ruan et al., 2000). Nicotine attenuates deficits in spatial learning in rats chronically exposed to lead (Zhou and 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 it 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 (Grove 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 of 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 affected by nicotine is BDNF, which plays a principal role in the expression and support of synaptic plasticity.

**Fig. 4.** E-LTP of area CA1 was absent in rats sleep deprived for 24 (A) and 48 hours (B). Nicotine treatment completely prevented SD-induced blockade of E-LTP. Each point is the mean ± S.E.M. from four to seven rats. *Points significantly different from all other groups. Details are as in Fig. 1. (Adapted from Aleisa et al., 2011).
including LTP (Figuero 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; Machaalan and Chen, 2018). BDNF produces its positive effects on neuronal development, growth and synaptic plasticity through activation of tyrosine kinase receptor B (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 (Ernfron and Bramham, 2003).

Most studies have provided 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; for review, see Machaalan and Chen, 2018). The expression of BDNF and its tyrosine kinase receptor B 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 laboratory, as well as others, have shown that chronic nicotine treatment prevented memory deficits seen in animal models of AD, stress, hypothyroidism, sleep deprivation, schizophrenia among others, likely by preventing impairment of LTP.

**Authorship Contributions**

Wrote or contributed to the writing of the manuscript: Alkadhi.

**References**


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