Brain derived neurotrophic factor (BDNF), its tyrosine kinase receptor B (TrkB) and nicotine.

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ABSTRACT

Nicotine is the major neurotoxicant in cigarettes that affects many transmitter systems within the brain as well as other factors, including the growth factors. Brain derived neurotrophic factor (BDNF), is the most abundant growth factor in the brain and plays a critical role in early new neuron differentiation, development and synapsis growth, and the survival of fully developed neurons and synaptic activity. Over the past 3 decades, data has emerged on the effects of nicotine and cigarette smoke exposure on the expression of BDNF and its primary specific receptor tyrosine kinase receptor B (TrkB). This review summarizes data regarding the changes in brain BDNF expression after nicotine or cigarette smoke exposure, and discusses their implications considering BDNF's functional roles.

Keywords: animal models, cigarette smoke exposure, nicotine, neurotrophic factor, infant, NTRK2.

Introduction

Brain derived neurotrophic factor (BDNF), is the most abundant neurotrophin growth factor in the brain and is important for cellular growth, development, survival and synaptic activity (Webster et al., 2002, reviewed Cunha et al., 2010). These actions are mediated via BDNF binding selectively to its tyrosine kinase receptor B (TrkB) receptor (Fayard et al., 2005).

Cigarette smoke exposure is the leading modifiable health burden in many countries with an estimated 1.1 billion people smoking in 2015 (WHOa). The consequences are not only on the smokers themselves, but also to those around them via passive smoke exposure, responsible for 7 million deaths per year, including 600,000 from second-hand smoking (WHOb). In addition, smoking is particularly detrimental on the developing young brains if exposed during the gestational period where the effects could be long lasting well into adulthood by causing epigenetic changes (reviewed Poon and Leibowitz 2016).

Our laboratory's interest is on Sudden Infant Death Syndrome (SIDS), for which cigarette smoke exposure is currently the leading modifiable risk factor (Mitchell et al., 2012). This is despite health campaigns advising against it (Mitchell et al., 2012). Although many pregnant women aim to cease smoking during pregnancy, the success rate is low during gestation (Filion et al., 2011). In addition, the relapse rate is high particularly in the early post-natal period. A main hypothesis in SIDS is that it is a developmental disorder of the cardio-respiratory centres in the brainstem (Hunt 1992) and as such, death ensues during a sleep period of either or both a cardiac or respiratory compromising event. BDNF knockout mice show severe depression of respiratory frequency and minute ventilation, with a loss of the hypoxic ventilatory drive, and they die within the first two weeks of life (Balkowiec and Katz, 1998, Erickson et al., 1996, Ernfors et al., 1994). This made it a candidate marker for study in our laboratory within the context of SIDS (Tang et al., 2012).

Nicotine, a main neuroactive component of cigarettes (tobacco), has been shown to directly induce changes in BDNF levels (Summarised in Table 2). In living humans, changes in BDNF are measured via serum or plasma given there is not yet a means to sensitively and accurately visualise and measure BDNF levels in the brain using imaging systems (Fukuchi et al., 2017). Despite this, evidence exists that peripheral (serum and plasma) BDNF levels do correlate with brain BDNF levels (Karege et al., 2002, Klein et al., 2011) and as such, can be used as surrogates of brain changes. That said, verification is advantageous and to this end, animal studies provide such assurance. Over the past three decades, many animal models of cigarette smoke and/or nicotine exposure have been developed and studied in relation to the effects on BDNF and TrkB expression

in the brain. This review will summarise these studies and aim to provide a mechanistic explanation for the changes observed.

The BDNF System

Growth factors are required for the normal development and functioning of the central nervous system. One family of growth factors is the neurotrophin family, which consists of nerve growth factor (NGF), BDNF, neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5). Neurotrophins are known for their roles during development and maintenance of the nervous system and have been detected as early as during embryonic development (reviewed in Bernd, 2008).

All neurotrophins are synthesised as pre-pro-neurotrophin precursors (approximately 240-260 amino acids long) within the rough endoplasmic reticulum and undergo several processes to convert into pro-neurotrophins and neurotrophins (Edwards et al., 1988; Seidah et al., 1996). Once formed they then accumulate in the membrane stacks of the trans-Golgi network and are secreted via two different types of secretory vesicles (constitutive or regulated) available for intracellular protein trafficking. The secretory vesicles are characterised according to their mechanism of secretion. The constitutive secretory vesicles release the neurotrophins in the absence of any specific triggering mechanism, whereas the regulated secretory vesicles release neurotrophins in an activity-dependent manner or in response to the stimuli, such as stress and hypoxia (reviewed by Cunha et al., 2010). Pro-neurotrophins not only promote the synthesis of neurotrophins, but can also act as ligands, with both often having opposing effects.

BDNF Production

As a neurotrophin, BDNF consists of two forms, pro and mature. Throughout the literature, the terms mature-BDNF, rh-BDNF, and BDNF are used interchangeably, but refer to the same form. Therefore in this review, the term BDNF will be used when referring to these. The pro- and mature-forms differ in function, primarily due to the neurotrophin receptors they activate. BDNF is generated from proBDNF by cleaving to extracellular proteinase plasmin (Pang et al., 2004) and undergoes N-terminal cleavage within the trans-Golgi network and/or immature secretory vesicles (Mowla et al., 2001). The intracellular conversion of proBDNF to BDNF is predominantly mediated by prohormone convertase (Seidah et al., 1996, Ullal et al., 2007). ProBDNF and BDNF play opposing roles by binding to two structurally unrelated receptors, the p75 neurotrophin receptor (p75NTR) and the TrkB, respectively (Chao, 2003; Patapoutian and Reichardt, 2001). ProBDNF through the activation of p75NTR facilitates apoptosis (Teng et al., 2005), whereas

BDNF through the activation of the TrkB receptor, promotes neuronal survival and axonal growth (Rose et al., 2004).

Once formed, BDNF is stored in the nerve terminals (Luo et al., 2001) and secreted through the regulated secretory pathway in an activity-dependent manner. Activity-dependent release of BDNF may be triggered by direct activation of voltage-gated Na2+ channels, which requires both Ca2+ influx and mobilization of Ca2+ from intracellular stores (Balkowiec and Katz, 2002). BDNF is transported both retrogradely and anterogradely (Ernfors et al., 1994, Tonra, 1999, Zhou and Rush, 1996). Anterograde transport is performed by sensory neurons towards both peripheral and central targets (Zhou and Rush, 1996), whereas the retrograde transport is used for target derived neurotrophic support (Tonra, 1999).

TrkB Receptor

The cellular actions of BDNF are mediated through the activation of its receptors. ProBDNF and BDNF bind selectively to TrkB and to p75NTR. BDNF binds to TrkB with high affinity and to p75NTR with low affinity, whereas proBDNF binds primarily to p75NTR and secondarily to TrkB, but not to TrkA or TrkC (Fayard et al., 2005). Given this review is focused on BDNF alone, the remainder of this section will only address TrkB.

The activation of TrkB receptors is a two-step process; ligand-mediated oligomerization of receptor molecules at the cell surface, followed by autophosphorylation of their tyrosine residues in the cytoplasmic domain (Schlessinger and Ullrich, 1992, reviewed in Cunha et al., 2010). Autophosphorylation promotes recruitment of a series of intracellular proteins and triggers signal transduction pathways (Patapoutian and Reichardt, 2001). After BDNF binds to TrkB at the cell surface, Na+ channels open. Once this has taken place, phosphorylation of Trk kinase activates phospholipase C-γ (PLC-γ), resulting in,

1- The formation of the second-messengers diacylglycerol and inositol 1,4,5 triphosphate (IP3) (Rose et al., 2004). IP3 induces the release of Ca2+ stores, increasing intracellular levels of Ca2+ thereby activating several pathways that are controlled by Ca2+ (Patapoutian and Reichardt, 2001), and;
2- The opening of transient receptor potential ion 3 channels (TRPC3) which are located adjacent to the TrkB receptors, and causes an influx of Na+ and Ca2+ leading to the modulation of synaptic transmission (Rose et al., 2004, reviewed in Cunha et al., 2010, schematically provided Figure 1).

The deletion of TrkB via knockout technology reduces presynaptic and postsynaptic development, and electrophysiological responses. These effects indicate that TrkB has a role in excitatory synaptic formation (Luikart et al., 2005). TrkB knockout mice died within 24 to 48 hours of birth and this was attributed to their failure to feed due to abnormalities (predominantly increased apoptotic cell death (Alcañtara et al. 1997, Holm et al. 2003)) in the motor neural system involved in swallowing (Klein et al., 1993). This indicates the critical role of TrkB in survival and brain apoptotic regulation. Moreover, differential regulation of TrkB has been found in many neuropathological conditions across various age spectrums with downregulation generally observed in neuro-psychiatric, -degenerative and -dependent disorders, while upregulation is seen in tumour related disorders and tissue injury (reviewed Gupta et al., 2013).

Physiological functions of BDNF

BDNF is involved in the promotion of normal nervous system development, through promoting neurite growth and establishing synaptic connections between neurons and target cells (Cohen-Cory, 2002), and via the interaction with other major neurotransmitter systems including glutamatergic, gabaergic, serotoninergic and dopaminergic (reviewed Changeux 2012, Autry and Montegia 2012). During development, high levels of BDNF expression are required for the normal development of the nervous system (Webster et al., 2002). Once the nervous system is developed, maintenance and stabilisation is promoted through the process of long-term potentiation (LTP). LTP is defined as "a stable, relatively long lasting increase in the magnitude of a post-synaptic response to a constant afferent volley following brief tetanic stimulation of the same afferents" (Teyler and DiScenna, 1987). Thus, it is where synaptic activity between brain cells occurs, leading to the formation of plasticity and memory (Ernfors and Bramham, 2003). BDNF has been shown to be important in promoting LTP (Korte et al., 1996) and the presence of BDNF can significantly improve LTP deficits in basal synaptic transmission in BDNF null mice (Patterson et al., 1996). The effects of BDNF on LTP are mediated by cAMP-response-element-binding protein (CREB) that regulates the expression of genes involved in the function of LTP (Ernfors and Bramham, 2003).

Physiologically, identified through BDNF knockout (KO) mice models, BDNF is important for the regulation of:

1- Respiration: BDNF KO mice showed severe depression of respiratory frequency and minute ventilation, with a loss of the hypoxic ventilatory drive (Balkowiec and Katz 1998, Erickson et al., 1996);

2- Coordination of movement and balance: BDNF KO mice had poor motor coordination and body balance (Conover et al., 1995);
3- Survival during early postnatal period: BDNF KO mice failed to thrive beyond postnatal day 8 (Conover et al., 1995, Ernfors et al., 1994, Jones et al., 1994).

These functions were affected predominantly as a result of increased neuronal apoptosis (Bianchi et al. 1996, Ernfors et al., 1994, Patel and Krimm 2010), decreased differentiation (Jones et al., 1995), and deficits in synaptic function/ synaptogenesis (Korte et al., 1996, Patterson et al., 1996), particularly in the thalamus (Lotto et al. 2001), substantia nigra (Baker et al. 2005), cerebellum (Schwartz et al. 1997) and sensory ganglia that innervate the inner ear and vestibular system (Bianchi et al. 1996, Ernfors et al., 1994). The death of the BDNF KO mice during the early postnatal period is believed to be due to the increased death of sensory neurons in the petrosal and nodose ganglia (Jones et al., 1994), given they relay information from the heart, lungs, great blood vessels, and gut to the central nervous system.

The expression and modulation of BDNF are regulated by various insults including stress, hypoxia, ischemia, seizure activity, temperature change, hypoglycaemia, and exposures to neurotoxic drugs (Reviewed in Tapia-Arancibia et al., 2004). Such changes in BNDF expression are also responsible for neurological conditions, such as anxiety, depression, epilepsy, Alzheimer's and Parkinson's disease. Indeed, abnormal immunostaining results of both BDNF and TrkB have been reported in the hippocampus of patients with schizophrenia (Iritani et al., 2003). This review will focus on the changes of BDNF and TrkB expression induced by nicotine exposure.

Nicotine and nicotinic acetylcholine receptors (nAChRs)

Nicotine is the major addictive and neurotoxic agent of cigarettes/tobacco (Dani and Heinemann 1996, Benowitz 1996), and unlike many of the compounds present in tobacco smoke, has no major environmental sources other than tobacco. Nicotine dependence is more prevalent than dependence on any other substance of abuse (Markou 2008), especially when tobacco is legal to consume and sell compared with the other substances. Nicotine's predominant effects are induced by activating the nAChRs. The nAChRs belong to the cys-loop family of ligand-gated ion channels that exist as pentamers of subunits, arranged symmetrically around a central pore (Cooper et al., 1991). A total of seventeen subunits (α1-10, β1-4, ε, γ and δ) have been identified, and all subunits are of mammalian origin with the exception of α8 which is avian (Papke et al., 2008). nAChRs are found at skeletal neuromuscular junctions and autonomic ganglia as either homopentamers or heteropentamers. Within the central nervous system, the predominant conformation of these

subunits is heteromeric, although α7 and α9 homopentamers exist. The α7 homomeric and α4β2 heteromeric nAChRs are the two main types widely expressed throughout the whole brain with the α7 nAChRs characterized by a fast activation, low affinity and high Ca^{2+} permeability while the α4β2 are characterised by a high affinity and slow desensitization. The expression of other nAChR subunits are more restricted within the brain (Reviewed Gotti and Clementi 2004).

Normal synaptic activity in the brain relies on the nAChRs via their response to endogenous acetylcholine (ACh), and have been implicated in physiological functions such as sleep, fatigue, anxiety, the central processing of pain, food intake and a number of cognitive functions (Role and Berg, 1996, Gotti et al., 1997, Lindstrom, 1997). However, abnormal (either excessive or deficient) ACh innervation of the nAChRs can lead to various diseases throughout the life span including frontal lobe epilepsy (Steinlein, 2000), schizophrenia (Freedman et al., 2000) and Alzheimer's disease (Wang et al., 2000).

The activation of brain nAChRs by nicotine also results in abnormal synaptic activity and changed neuropathology (reviewed in Slotkin, 1998), including addiction, increased apoptosis (cell death) (Trauth et al., 2000, Machaalani and Waters, 2005), and abnormal expressions of neurotransmitters and their receptors such as glutamate (Fanous et al., 2006), serotonin (Say et al., 2007), orexin (reviewed by Machaalani et al., 2016), and dopamine (Slotkin, 1998). The latter is thought to be associated with increased endorphin levels and increased addiction to nicotine. Moreover, a direct change in the expression (Browne et al., 2010, Vivekanandarajah et al., 2015, Vivekanandarajah et al., 2016) and functions (Sparks and Pauly, 1999, Buisson and Bertrand, 2001) of the nAChRs occur in response to nicotine exposures.

Human studies of nicotine on BDNF and TrkB

The majority of the human studies of nicotine's effects on BDNF involve DNA genotyping for BDNF SNP variants. Such studies where adult smokers were genotyped found several associations between allelic variations of BDNF and nicotine dependence, yet some variations were evident according to sex and ethnicity (Beuten et al., 2005, Lang et al., 2007, Zhang et al., 2012, 2015, 2016). Two other studies extended the analysis into the offspring of smoking mothers and found the associations between BDNF SNP variants and addiction were indeed present in adolescents (Toledo-Rodriguez et al. 2010, Lotfipour et al., 2009). Such adolescent offspring had a 1.5-fold increase in substance abuse (Lotfipour et al., 2009). Only one study has looked at the effects of nicotine exposure on TrkB in humans and this study was also a genotype study of 9 SNPs within

the TrkB gene (NTRK2). An association between the allelic variants of NTRK2 and three nicotine dependence measures were found in European-American smokers (Beuten et al., 2007).

Given the limitations in directly studying brain BDNF in living humans, BDNF levels have primarily been studied in the periphery, via serum or plasma. Peripheral BDNF is highly concentrated in the platelets (Fujimura et al., 2002), with serum having approximately 50–200-fold higher levels than the plasma (Radka et al., 1996, Rosenfeld et al., 1995). This difference is suggested to reflect the release of BDNF from platelets during blood clotting (Fujimura et al., 2002). This could also explain why BDNF levels were found to vary according to diurnal rhythm in plasma but not in serum (Piccinni et al., 2008), and to decrease with aging or weight gain in plasma but not in platelets or serum (Lommatzsch et al., 2005). Regarding brain levels, derived from animal studies, peripheral and brain BDNF levels do correlate, yet this was species dependent; yes in the rat and pig, but no in the mouse (Karege et al., 2002, Klein et al., 2011). However, Klein et al., 2011 suggest that the lack of any trace of BDNF in mouse blood may not be a true finding, but rather due to the low sensitivity of the commercially available ELISA kit. This is based on the finding that mice readily transport iodine-labelled BDNF and recombinant BDNF in the blood (Pan et al. 1998). Nevertheless, based on the strong evidence from the studies in the rat and pig, it can be extrapolated that peripheral (serum and plasma) measures of BDNF in the human would be representative of brain levels.

To date, six studies have been conducted in humans to determine the effects of nicotine (via cigarette smoking) on peripheral BDNF levels (summarised in Table 1). From these studies, the predominant direction of change due to nicotine exposure is increased BDNF (Zhang et al., 2010, Suriyaprom et al., 2013, Jamal et al., 2015, Neves et al., 2017). The initial two studies performed by Kim et al. and Bhang et al. were performed on plasma with relatively small sample size and showed that healthy adult smokers had decreased plasma BDNF than the non-smokers; when smoking was ceased for > 4 weeks, BDNF levels increased to the non-smoker's levels or above (Kim et al., 2007, Bhang et al., 2010). The subsequent studies performed on serum with larger sample size showed that both schizophrenic (Zhang et al., 2010) and healthy adults (Suriyaprom et al., 2013, Jamal et al., 2015, Neves et al., 2017) had increased serum BDNF levels and this was associated /correlated with the amount and duration of cigarette smoking and blood cortisol levels, but not with the BDNF Val66Met genotype (Suriyaprom et al., 2013). Combined, these studies provide strong evidence that nicotine exposure in humans affects BDNF expression and this is most likely to be a consequence of the changes in brain BDNF levels, something that animal studies have helped to clarify as discussed in the next section.

Our laboratory was the first to report BDNF and TrkB expression in the human infant brain (brainstem and hippocampus) (Tang et al., 2010) and subsequently to report the effects of cigarette smoke exposure amongst these infants, for whom the predominating diagnosis was Sudden Infant Death Syndrome (SIDS) (Tang et al., 2011). We found that infants for whom, at the time of death, the parents had indicated a positive history of cigarette smoke exposure (be it the mother, father, both or any other household member), no change in BDNF expression was observed in the brainstem nuclei studied, yet an increase in proBDNF and decrease in TrkB was evident in the hypoglossal and vestibular nuclei, both having a role in respiratory control (Tang et al., 2011). A subsequent study from another laboratory showed that in the kolliker-fuse nucleus (also important for respiratory control), altered BDNF expression was evident amongst infants with cigarette smoke exposure (Lavezzi et al., 2014) and this was extended into the cerebellum showing decreased BDNF levels in both brain regions (Lavezzi et al., 2018). Combined, these studies provide the first reports that exposure of the developing human to pre- and/or postnatal cigarette smoke alters BDNF and TrkB expression in respiratory regulating regions and could have played a role in subsequent pathophysiology changes leading to death.

Animal models of nicotine and cigarette smoke exposure

Given the limitations of studying brain BDNF in humans, animal studies are developed to provide the much needed data. With regards to nicotine exposure, to ensure the animals are receiving doses that equate to human consumption, measures of either nicotine or cotinine levels in the blood or urine are performed, with measurement of cotinine preferred given its longer half life (16 hours versus 2 hours for nicotine)(Benowitz and Jacob, 1993). The metabolism, distribution and excretion rate of nicotine differs with species, hence slight variations would be anticipated (Bramer and Kallungal 2003). To mimic childhood and adult cigarette smoke exposure paradigms, doses should be approximately 6mg/kg/day to produce cotinine levels indicative of active smoking which is >220ng/ml or 100nmol/L in serum and >3516ng/ml or 1,700nmol/L in urine (Vine et al., 1993, SSWPS Handbook 2014). For early postnatal exposure, as would be experienced by babies through breast milk or environmental passive smoke exposure, the dose should be within 2-4mg/kg/day resulting in plasma and urine cotinine levels >5ng/ml and >10ng/ml respectively (Luck and Nau, 1985). For maternal (prenatal) cigarette smoke exposure, doses should be within 2-6mg/kg/day, resulting in plasma cotinine levels of >100ng/ml (Murrin et al., 1987, Lichtensteiger et al., 1988).

The mode of administration is another consideration when developing the animal model of nicotine exposure. The common methods to date include: gavage, injection (intraperitoneal or

subcutaneous), infusion, osmotic minipump infusion, dermal patches or placing the animal in a cigarette smoke exposure chamber. Current studies lean towards the use of minipumps and nicotine patches given they result in steady states of plasma nicotine levels and overcome the hypoxia-ischemia effects which were seen to occur when using the injection method (Slotkin 1998). A recent review addressing the various animal models of nicotine exposure and their results is provided by Cohen and George 2013.

Nicotine exposure on BDNF expression in the brain from animal studies (Table 2).

The baseline expression of BDNF has been extensively studied amongst species including the rat pup, (Hafidi et al., 1999), piglet (Pieris et al., 2004, Tang et al., 2008), gerbil (Tierney et al., 2001), adult rat (Hafidi et al., 1999, Kawamoto et al., 1996, Yan et al., 1997), adult monkey (Kawamoto et al., 1999, Zhang et al., 2007), human infant (Tang et al., 2010, Tang et al., 2011), and human adult (Murer et al., 1999, Tang et al., 2010).

To date, a modest number of studies have examined the effects of nicotine or cigarette smoke exposure, both prenatally and postnatally, on the expression of BDNF within the brain (summarized Table 2). Majority of the studies in Table 2 were conducted in the rat and mouse with the exception of our own study in piglets (Tang et al., 2008). Moreover, the majority focused on the male sex and adult age. It is only recently (since 2011) that studies have commenced to look at the effects of prenatal nicotine exposure on BDNF expression in the offspring (Table 2). The expression of BDNF was measured at both mRNA and protein levels, and were via real-time polymerase chain reaction (RT-PCR), *in situ* hybridisation (ISH), western blotting (WB), immunohistochemistry (IHC), and enzyme-linked immunosorbent assays (ELISAs). The main brain regions studied included the hippocampus, prefrontal cortex (PFC), and dorsal striatum (dSTR), with a few studies on the nucleus accumbens (NAc) within the basal forebrain, and our own being the only one on the brainstem (Tang et al., 2008). The rationale for the study of these brain regions relates to the addictive nature of nicotine and interplay with the dopaminergic, glutamatergic and Gabaergic systems (PFC, dSTR and NAc) (Reviewed Feduccia et al., 2012), and the role of nicotine in affecting LTP (hippocampus) and respiratory control (brainstem).

As shown in Table 2, the paradigms of nicotine exposure vary considerably including the age, dose, duration, and method of exposure. All these not surprisingly, lead to differing outcomes. In general, there is a consensus that BDNF expression increases after pre- and post-natal nicotine exposures in the NAc (Table 3), yet for the hippocampus, PFC and dSTR, an increase, decrease or no change in BDNF expression can occur (Table 3). Another contributing factor for the differences could be the

heterogeneous cell constituents and regions within each of these structures if they were studied on their own as shown by IHC and ISH, where specific subregional changes could be identified.

The effect of nicotine exposure on TrkB expression (Table 4)

The TrkB receptors have also been localised both pre- and post-synaptically, along axons, in synaptic terminals, and in the plasma membrane of dendritic spines and glial cells (Frisen et al., 1993). The localization of TrkB in the synaptic terminal is consistent with the role of TrkB as a mediator of retrograde transport of BDNF to neuronal cell bodies (Murer et al., 2001).

Much less has been reported regarding the effects of nicotine exposure on TrkB expression, with only 5 studies to date (summarised Table 4). All are in the adult brain (French et al., 1999, Sun et al., 2007, Formaggio et al., 2010, Xiao et al., 2015) with the exception of ours in the infant brains (Tang et al., 2008). The general finding seems to be increased TrkB expression in the hippocampus, cortex, and striatum (Table 3), but decreased levels in certain brainstem nuclei, the nucleus accumbens and the ventral tegmental area (Table 4).

Mechanism(s) involved in nicotine induced BDNF and TrkB changes

The expression of BDNF and TrkB are closely associated with nAChRs, however to date no studies have examined their colocalization. Evidence showing BDNF affecting nAChRs and vice versa predominantly relates to the α7 nAChRs. The injection of BDNF into cultured embryonic hippocampal (Massey et al., 2006) and adult cervical ganglionic neurons (Zhou et al., 2004) increased α7 nAChR expression, and increased the frequency of spontaneous synaptic currents within minutes (Zhou et al., 2004). Blocking α7 nAChRs leads to reduced BDNF mRNA expression in the hippocampus (Freedman et al., 1993). In contrast, exposing β2 nAChR knockout mice to nicotine had no effect on brain BDNF levels (Harrist et al., 2004). This suggests that the α4 component of the α4β2 nAChRs is the predominating component interacting with BNDF after nicotine exposure. This is somewhat in line with the finding that almost all reported human studies of nicotine dependence found no association of the gene for the nAChR β2 subunit (CHRNB2) with nicotine dependence (Li et al., 2005, Feng et al., 2004, Silverman et al., 2000, Lueders et al., 2002) but did so for the α4 subunit gene (CHRNA4) (Li et al., 2005, Feng et al., 2004, Hutchison et al., 2007). Subsequent analysis showed a strong interaction of CHRNA4 with BDNF and CHRNB2 with TrkB (Li et al., 2008).

Non-homology in BDNF and nAChRs expression changes have also been reported. In our laboratory using the infant piglet model of nicotine exposure, no change in BDNF protein

expression was observed in any of the brainstem nuclei studied (Tang et al., 2008) despite there being expression changes in α2, α3, α4, α7, α9, and β2 nAChR subunits (Vivekanandarajah et al., 2015). The converse was reported by Romano et al. where they found nicotine exposure increased BDNF mRNA in the hippocampus and cortex, but had no effect on the nAChR subunits α2, α4, α7, and β2 (Romano et al., 2014). Thus, it remains in question whether the changes in BDNF expression after nicotine exposure are entirely dependent on nAChR activation and if so, via which subunits and to what level of activation.

Based on the data and knowledge to date, we propose two mechanisms involved in nicotine induced changes of BDNF and TrkB (Figure 1). In the presence of nicotine, the nAChRs are activated, with the specific subunits dependent on the brain region. Upon binding, there is an influx of Ca2+ which causes an increased BDNF release with the precise mechanism still unknown, yet excitatory pathways via the n-methyl-d-aspartate receptor are implicated (Obrietan et al., 2002). This increases BDNF binding to TrKB, which leads to toxic levels of Ca2+ which then affects subsequent cascades that regulate cell survival and synaptic activity. Yet, nAChR desensitisation can occur with chronic nicotine exposures, thus reducing the activity of this pathway causing the opposite actions. A nAChR independent pathway is also feasible where nicotine causes direct epigenetic modifications to the BDNF gene which then affects the production of BDNF at both the mRNA and protein levels, thus decreasing the amount of BDNF release. For both mechanisms, a decrease in BDNF expression could be indicative of decreased neuroprotection to subsequent insults, or could be due to increased cell death. Increased BDNF expression could be indicative of increased neuroprotective mechanisms to counteract the 'threat'. Increased TrkB expression seen in most paradigms of nicotine exposure would be indicative of an adaptation to balance BDNF changes to maintain normal homeostasis of cell survival and synaptic activity.

Concluding remarks

From this review, the majority of the paradigms involving nicotine exposure result in either increased or decreased BDNF expression, and mostly increased or no change in TrkB receptor expression (Summarised in Table 3). However, the majority of studies were undertaken in the adult rat and predominantly in the hippocampus and prefrontal cortex. Thus, further studies are required to determine the changes at other developmental stages, such as prenatal and early postnatal periods, and across other brain regions, particularly in regions of respiratory control and coordination of balance and movement as BDNF affects these specific motor controls. A better understanding of BDNF and TrkB change in such brain regions could be of clinical significance, given the long lasting effects of pre-natal nicotine exposure on addictive behaviour in the offspring

in adulthood (Kendler et al., 2012). This will facilitate breaking the cycle of smoking from the parents to the offspring.

Figure Legends

Figure 1. Schematic of (1) BDNF activation of TrkB and the regulation of this process by (2) nicotine. (1) BDNF binds to TrkB which activates and causes adjacently located TRPC3 channels to allow the influx of Na+ and Ca2+, as well as opens the sodium and calcium channels to allow the entry of these ions. The entry of Na+ causes the phosphorylation of TrkB which activates PLCγ which then activates IP3 leading to increased intracellular Ca2+ levels. (2) In the presence of nicotine, the nAChRs are activated, with the specific subunits dependent on the brain region. On binding, there is an influx of Ca2+ which causes increased BDNF release. This has positive feedback on pathway 1 leading to toxic levels of Ca2+ which then affects subsequent cascades regulating cell survival and synaptic activity. nAChR desensitisation can also occur, thus reducing this pathway causing opposite effects. A nAChR independent pathway is also feasible via epigenetic modification of the BDNF gene to affect the production of BDNF and pathway 1.

Table 1- Human studies of nicotine exposure on BDNF system expression levels.

Exposure regime Age & sex	**N values**	**Sample & method**	**Findings**	**Reference**
Adult male smokers (at least 5 cigarettes/day for 9 years) before and after 2 months of smoking cessation	20 smokers vs 20 non-smokers; 12/20 ceased smoking unaided	Plasma, ELISA	↓ BDNF in smokers. Smoking cessation for 2 months, ↑BDNF	Kim et al., 2007
Smokers, and week 4 & 12 of smoking cessation	45 smokers vs 66 non-smokers; smokers ceased via varenciline (n=12), nicotine patch (n=21), & unaided (n=12). But only 19 maintained until week 12. Thus n=19 for plasma levels at week 4 and 12.	Plasma, ELISA	↓ BDNF in smokers. Smoking cessation ↑BDNF at 4 and 12 weeks, and did not differ according to cessation method.	Bhang et al., 2010
Adult male schizophrenia smokers	102 smokers vs 37 non-smokers	Serum ELISA	↑BDNF in schizophrenic smokers	Zhang et al., 2010
Adult male and female smokers (Ethnicity- Thai) (10-20 cigarettes/day for >14 years)	200 smokers vs 111 non-smokers	Serum ELISA	↑BDNF in smokers. Correlated with number of cigarettes smoked. No association between BDNF Val66Met genotype and serum BDNF.	Suriyaprom et al., 2013
Adult male and females	564 Never smokers, 690 former smokers, current smokers (non-dependent= 528 vs dependent= 306)	Serum, ELISA	↑BDNF in current smokers (both dependent and non having same levels)	Jamal et al., 2015
Adult male. Heavy smokers 20 cigarettes/day, vs light smokers 10 cigarettes/day	14 smokers (7 heavy, 7 light) vs 13 non-smokers	Plasma, ELISA	↑BDNF in heavy smokers and associated with lower cortisol levels at night	Neves et al., 2017

			time.	
Infants died suddenly within 1st year of life	45 exposed to cigarette smoke vs 12 non-exposed	IHC for proBDNF, mature BDNF, and TrkB in brainstem medulla	↑proBDNF in exposed, No-change for rhBDNF, ↓TrkB	Tang et al., 2011
Infants died suddenly within 1st year of life	12 exposed to cigarette smoke vs 4 non-exposed	IHC for mature BDNF, Kolliker Fuse nucleus brainstem	Altered expression	Lavezzi et al., 2014
Fetus and Infants who died suddenly	13 exposed to cigarette smoke vs 29 non-exposed	IHC for mature BDNF, cerebellum	↓ BDNF in exposed	Lavezzi et al., 2018

IHC, Immunohistochemistry, ND, nicotine dependence

Table 2 Summary of the effects of cigarette smoke and nicotine exposures on brain BDNF expression in animal models

Models	Developmental Stage when brain studied	Method & Brain region	Results	References
Postnatal exposure				
s.c. somotic minipump nicotine 2.3µl/h for 14 days	Aged (22-24 month) male rat	RT-PCR, Hippocampus, cortex, striatum	↓ non-significant trend hippocampus	Monteggia et al., 1994
Acute local infusion straight into hippocampus	Adult male rat	ISH; Hippocampus	No change	French et al., 1999
Acute & Chronic exposure [injection twice daily, 7 days]	Adult rat	ISH; Hippocampus	Acute-↓mRNA chronic- ↑mRNA	Kenny et al., 2000
Chronic exposure [s.c. 0.4mg/kg injection twice daily, 7 days]	Adult male rat	MALDI-TOF-MS, RT-PCR; Striatum	↓mRNA & protein	Yeom et al., 2005
Chronic exposure [1mg/kg, 2/day, 4-6 weeks]	Adult rat	WB; Hippocampus	↑protein of CA1	Aleisa et al., 2006
Chronic exposure 2mg/kg/day nicotine osmotic minipump for 14 days	Infant piglet	IHC, brainstem	No change	Tang et al., 2008
Chronic- Orally 6mg/kg/day from P1-P7	Infant (P8) mice	ISH; Hippocampus	↑mRNA	Son and Winzer-Serhan 2009
0.2mg/kg s.c. injection 2x/day for 5 weeks	Adult male rat	ELISA, hippocampus & cortex	↑protein both regions	Czubak et al., 2009
12cigarettes/ day 7 days/week for 60 days	Adult (2 month) male mice	ELISA, hippocampus	↓protein	Tuon et al., 2010
60–65 mg/kg/day oral (drinking water) for 7 weeks	Adult (12 weeks) male mice	ELISA; striatum (caudate-putamen), NAc, amygdala, VTA, substantia nigra	↑protein NAc	Kivinummi et al., 2011
Oral 6mg/kg/day starting P1	Neonatal (P5 & P8) male & female mice	ISH; Hippocampus	↑mRNA in males	Damborsky and Winzer-Serhan 2012
3 mg/kg nicotine i.p. injections 6 h before killing	Adult male mice	PCR- several bdnf transcripts; cortex	↑mRNA	Chase and Sharma 2013

Chronic low (6.3 mg/kg/day) vs high (18 mg/kg/day) nicotine osmotic minipump	Adolescence (4 weeks) mice	ELISA; striatum	↓protein in high exposure	Ortega et al., 2013
Oral nicotine (2h/day for 6 days 10mg/L nicotine) during adolescence (P37-42)	Adult (P180) male mice	RT-PCR; hippocampus & cortex	↑mRNA	Romano et al., 2014
Inhalation for 10 days during Infancy (P2-11) and teenage (P21-30)	Adult (P60)- mice	RT-PCR & WB; hippocampus & PFC	Infancy-↓mRNA hippocampus only; Teen- no change	Xiao et al., 2016
Cigarette inhalation 2x1hr/day from P3-P14	P15 (infancy), P35 adolescence) P65 (adulthood) mice	Immunoassay; hippocampus	infancy - ↓protein, adolescence and adult- no change	Torres et al., 2015
Cigarette inhalation 2x1hr/day & i.p nicotine 3-9mg/kg/day short (4 weeks) vs long term (12 weeks)	Adult rat	WB, IHC, cerebral cortex	↑protein	Naha et al., 2017
Prenatal exposure				
GD4 osmotic minipump nicotine 3mg/kg/day	Adolescence (P35) female Rats	RT-PCR & microarray; PFC, striatum, NAc, PVN, and the amygdala.	↑ mRNA NAc & striatum, ↓ PVN	Wei et al., 2011
0.05mg/kg/i.v. injection 3×/day from GD 8–21. weened P21	Adolescence (P35) male & female rats	ELISA; NAc, dSTR, PFC & hippocampus	↑ protein all regions	Harrod et al., 2011
Cigarette inhalation 4hr/day; 5days/week from GD4-parturition; offspring weaned P21	Adult (4 months) mice	RT-PCR; WB; striatum	↓mRNA & protein in males only. No difference amongst females.	Yochum et al., 2014
Single injection 66 µg/kg bodyweight for 5 days	Neonate-infancy male rat pups: group I P1-5, group II P5-10, group III P10-15.	ELISA & WB; hippocampus & frontal cortex	↓ in all groups for both regions	Xiaoyu et al., 2015
Inhalation GD10 for 10 days	Adult (P60)- mice	RT-PCR & WB; hippocampus &	↓mRNA both brain regions	Xiao et al., 2016

		prefrontal cortex		
0.05mg/kg/i.v. injection 3×/day from GD 8–21. weened P21	Adult (P90) male & female mice	ELISA; NAc, dSTR, PFC	↑ protein NAc & dSTR, ↓ in PFC	Lacy et al., 2016
Inhalation waterpipe tobacco 2h/day	Adult (20wks) rats	Immunoassay; hippocampus	↓protein	Al-Sawalha et al., 2017

Abbreviations: dSTR, the dorsal striatum; ISH, in situ hybridisation; MALDI-TOF-MS, matrix-assisted laser desorption/ionization- Time of Flight- Mass Spectrometry; NAc, nucleus accumbens; PFC, prefrontal cortex; PVN, periventricular nucleus of the hypothalamus; RT-PCR, reverse transcription-polymerase chain reaction; WB, western blot.

Table 3: The number of studies in Table 2 and 4 that report an increase, decrease or (-) no change in BDNF and TrkB expression in the specific brain region studied.

	BDNF		**TrkB**
	Postnatal	**Prenatal**	**Postnatal**
Hippocampus	6 ↑ (4 mRNA, 2 protein) 4 ↓ (3 mRNA, 2 protein) 2 – (1 mRNA, 1 protein)	1 ↑ (protein) 3 ↓ (1 mRNA, 2 protein)	3 ↑ (mRNA) 2 – (1 mRNA, 2 protein)
Prefrontal Cortex	4 ↑ (3 mRNA, 2 protein) 2 – (2 mRNA, 2 protein)	1 ↑ (protein) 3 ↓ (1 mRNA, 2 protein)	2 ↑ (3 mRNA, 1 protein) 3 – (2 mRNA, 3 protein)
Dorsal Striatum	2 ↓ (1 mRNA, 2 protein)	3 ↑ (1 mRNA, 2 protein) 1 ↓ (mRNA & protein)	1 ↑ (mRNA)
Nucleus Accumbens	1 ↑ (protein)	3 ↑ (1 mRNA, 2 protein)	1 ↓ (mRNA & protein) 1 – (mRNA & protein)

Values in brackets indicate the changes that occur at the mRNA or protein level. Where the total is greater than the summary value, this indicates a study would have looked at both mRNA and protein.

Table 4: Summary of the effects of cigarette smoke and nicotine exposures on brain TrkB receptor expression in animal models

Models	Developmental Stage when brain studied	Method & Brain region	Results	References
Postnatal exposure				
Acute local infusion straight into hippocampus	Adult male rat	ISH; Hippocampus	↑mRNA	French et al., 1999
Osmotic minipump 3.15 mg/kg/day for 7 days	Adult rat	RT-PCR; WB; PFC, Striatum, NAc, Amygdala, medial basal hypothalamus, Hippocampus, VTA	↑mRNA in PFC, striatum, ↓mRNA in NAc & VTA ↑protein in PFC, MBH, ↓protein in NAc & VTA	Sun et al., 2007
Chronic exposure 2mg/kg/day nicotine osmotic minipump for 14 days	Infant piglet	IHC, brainstem	↓protein	Tang et al., 2008
Osmotic minipump 1.2 mg free base/kg/d, for 7 days.	Age not indicated; rat	RT-PCR; WB; Cerebral cortex, basal forebrain	No change.	Formaggio et al., 2010
Inhalation for 10 days during Infancy (P2-11) and teenage (P21-30)	Adult (P60)- mice	RT-PCR & WB; hippocampus & prefrontal cortex	Exposure in infancy- ↑mRNA hippocampus only; Teen- no change	Xiao et al., 2016
Prenatal exposure				
Inhalation GD10 for 10 days	Adult (P60)- mice	RT-PCR & WB; hippocampus & prefrontal cortex	↑mRNA both brain regions	Xiao et al., 2016

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Figure 1

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