*Current Perspective***The Roles of Glial Cell Line-Derived Neurotrophic Factor, Tumor Necrosis Factor- α , and an Inducer of These Factors in Drug Dependence**Minae Niwa^{1,2}, Atsumi Nitta¹, Kiyofumi Yamada^{1,3}, and Toshitaka Nabeshima^{1,2,*}¹Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine, Nagoya 466-8560, Japan²Department of Chemical Pharmacology, Meijo University Graduate School of Pharmaceutical Sciences, Nagoya 468-8503, Japan³Laboratory of Neuropsychopharmacology, Division of Life Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kanazawa 920-1192, Japan

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Abstract. There are few efficacious medications for drug dependence at present. Recent evidence has suggested that various cytokines are involved in the effects of abused drugs, suggesting that these factors play a role in drug dependence. In this article, the roles of glial cell line-derived neurotrophic factor (GDNF) and tumor necrosis factor- α (TNF- α) in drug dependence are discussed. GDNF inhibits the cocaine-induced upregulation of tyrosine hydroxylase activity in the ventral tegmental area and blocks behavioral responses to cocaine. TNF- α attenuates rewarding effects and locomotor sensitization induced by methamphetamine (METH) and morphine (MOR). Moreover, we mentioned the potential of Leu-Ile, which induces the expression of GDNF and TNF- α , as a novel therapeutic agent for drug dependence. Leu-Ile inhibits not only the development but also the maintenance of METH- or MOR-induced place preference and locomotor sensitization in mice. The inhibitory effect of Leu-Ile on METH- or MOR-induced place preference is not observed in GDNF heterozygous and TNF- α knockout mice. Leu-Ile inhibits METH- or MOR-induced place preference and sensitization by attenuating the METH- or MOR-induced increase in extracellular dopamine levels in the nucleus accumbens via the induction of GDNF and TNF- α expression. These findings suggest that Leu-Ile could be a novel therapeutic agent for drug dependence.

Keywords: glial cell line-derived neurotrophic factor, tumor necrosis factor- α , methamphetamine, morphine, Leu-Ile

Introduction

Drugs of abuse are able to elicit compulsive drug-seeking behaviors upon repeated administration, which ultimately leads to the phenomenon of addiction (1). In terms of lost lives and productivity, drug addiction remains one of the most serious threats to a nation's public health (2). There are currently few efficacious medications for drug dependence. Recently, it has been reported that BP897, a dopamine (DA) D₃-receptor

partial agonist, affects cocaine-associated stimulus-induced drug-seeking behavior in rats (3). The opioid κ -receptor agonist TRK-820 inhibits not only the rewarding effects of morphine (MOR) and cocaine, but also a mecamylamine-precipitated nicotine-withdrawal aversive effect (4). These medications should be effective even when they are administered after the development of drugs of abuse.

Cytokines, which are known to influence synaptic transmission and neuronal morphology (5), may be involved in alterations of the morphology of dendrites and their spines in the prefrontal cortex, nucleus accumbens (NAc), and hippocampus after repeated injection of psychostimulants (6, 7). Glial cell line-

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derived neurotrophic factor (GDNF) inhibits the cocaine-induced upregulation of tyrosine hydroxylase (TH) activity in the ventral tegmental area (VTA) and blocks behavioral responses to cocaine (8). Furthermore, we have previously demonstrated that tumor necrosis factor- α (TNF- α), an inflammatory cytokine, attenuates rewarding effects and locomotor sensitization induced by methamphetamine (METH) and MOR (9, 10). Taken together, GDNF and TNF- α would be candidates for therapeutic agents against drug dependence. However, there are serious obstacles to their therapeutic application: it is difficult to deliver GDNF from the periphery to the brain, since it is a macromolecule that cannot penetrate the blood-brain barrier (11), and is easily broken down by proteases in the blood stream. In addition, TNF- α damages the peripheral tissues, because it triggers the expression of other cytokines (12). Therefore, GDNF and TNF- α cannot be used directly as therapeutic tools for drug dependence. We hypothesized that a low-molecular-weight compound, which can easily penetrate the blood-brain barrier and induces production of GDNF and TNF- α in the brain, could be a novel therapeutic agent for drug dependence.

Roles of GDNF in drug dependence

GDNF produced by a glial cell line is a factor that plays important roles in the dopaminergic neurons (13). GDNF promotes the survival and function of DA neurons *in vivo*, in both the intact rat brain and after nigrostriatal lesioning (14, 15). It has been also shown that GDNF is secreted in the target (striatum) and transported retrogradely to the DA cell bodies in the mesencephalon (16). These findings suggest that GDNF could be effective against dopaminergic degeneration, and is expected to be useful for dopaminergic neurological disorders.

Transplantation of simian virus-40 glial cells, which produces and secretes GDNF, or delivery of GDNF-conjugated nanoparticles into dorsal and ventral striatum impairs the acquisition of cocaine self-administration in rats (17, 18). The upregulation of the GDNF pathway in the midbrain, is the molecular mechanism by which the putative anti-addiction drug ibogaine mediates its desirable action of reducing ethanol consumption (19). Infusion of GDNF into the VTA blocks certain biochemical adaptations (induction of TH, NR1 subunit of *N*-methyl D-aspartate receptors, Δ FosB, and protein kinase A catalytic subunit) to chronic cocaine or MOR treatment as well as cocaine-induced place preference (8). Conditioned place preference (CPP) paradigm, in which animals learn the association of an environment paired with drug exposure, is usually used as a measure

of the rewarding properties of abused drugs (8–10). Conversely, responses to cocaine are enhanced in rats by intra-VTA infusion of anti-GDNF antibody and in GDNF heterozygous knockout mice (8). Chronic exposure to cocaine or MOR causes a dramatic decrease in GDNF signaling as evidenced by a 65%–70% reduction in the levels of tyrosine-phosphorylated Ret in the VTA (8). Taken together, these findings support the scheme that the drug-induced decrease in GDNF signaling in the VTA removes a homeostatic feedback (or counteracting) mechanism on this neural pathway and thereby contributes to sensitized biochemical and behavioral responses to drugs of abuse.

Roles of TNF- α in drug dependence

TNF, a potent proinflammatory cytokine, plays a critical role in the immune response that leads to effective clearance of a variety of pathogens or to immunopathology and autoimmune disease (20). TNF- α also affects the central nervous system (CNS) directly or indirectly through the stimulation of vagal afferents (21). Thus, this cytokine is emerging as a modulator of CNS function. Regarding the behavioral effects of TNF- α , transgenic mice expressing high levels of TNF- α in the brain show several changes in exploratory activity and emotional behavior in association with reduced TH immunoreactivity in the striatum without neuronal cell death (22). In contrast, mice with targeted deletions of the TNF- α gene (TNF- α knockout mice) show anxiogenic-like behavior accompanied by an increase in serotonin metabolism (23).

METH or cocaine induces the expression of TNF- α mRNA in human brain endothelial cells (24, 25). METH induces the expression of TNF- α mRNA and protein in the NAc, striatum, hippocampus, and amygdala of rats (9). Expression of the TNF- α in the brain of mice is induced 3 h after METH injection and remains elevated for up to 6 h of METH exposure (26). Repeated METH or MOR treatment increases TNF- α mRNA and protein levels in neurons of the NAc through the activation of DA receptors (9, 10). Recently, we have demonstrated that TNF- α plays a neuroprotective role in METH-induced dependence and neurotoxicity (9) (Table 1). Moreover, we have found that TNF- α inhibits MOR-induced rewarding effects and sensitization to the locomotor-stimulating effects, which is argued to reflect one neuroadaptive process associated with dependence (10) (Table 1). Conversely, responses to METH or MOR are enhanced in TNF- α knockout mice. Furthermore, TNF- α attenuates the repeated METH or MOR treatment-induced increase in extracellular DA levels in the NAc (9, 10). TNF- α itself potentiates synaptosomal and

Table 1. Summary of the effects of TNF- α on methamphetamine- or morphine-induced changes in biomarkers and behavior

	Methamphetamine	Morphine
TNF- α mRNA		
Single	$\pm$	$\pm$
Repeated	$\uparrow$	$\uparrow$
Conditioned place preference		
Wild type	$\uparrow$	$\uparrow$
Wild type + TNF- α	$\downarrow$	$\downarrow$
TNF- α (-/-)	$\uparrow\uparrow$	$\uparrow\uparrow$
TNF- α (-/-) + TNF- α	N.D.	$\downarrow$
Hyperlocomotion (Single)		
Wild type	$\uparrow$	$\uparrow$
Wild type + TNF- α	$\downarrow$	$\uparrow$
TNF- α (-/-)	$\uparrow$	N.D.
Locomotor sensitization (Repeated)		
Wild type	$\uparrow$	$\uparrow$
Wild type + TNF- α	$\downarrow$	$\downarrow$
TNF- α (-/-)	$\uparrow\uparrow$	N.D.
Extracellular dopamine levels		
Wild type	$\uparrow$	$\uparrow$
Wild type + TNF- α	$\downarrow$	$\downarrow$

$\pm$, No change; $\uparrow$, Significant increase; $\downarrow$, Significant decrease; N.D., Not determined.

vesicular DA uptake and diminishes the METH-induced decrease in synaptosomal and vesicular DA uptake (9). These findings suggest that TNF- α plays a neuroprotective role in METH- or MOR-induced dependence by activating plasmalemmal DA transporter as well as vesicular monoamine transporter-2 and by inhibiting METH- or MOR-induced DA release (9, 10) (Table 1).

Effects of Leu-Ile, an inducer for GDNF and TNF- α , on METH-induced dependence

GDNF and TNF- α inhibit drug-induced dependence and would be candidates for therapeutic agents against drug dependence. Furthermore, a previous study has demonstrated that inflammatory stimuli such as TNF- α and lipopolysaccharide induces the synthesis of GDNF cultured astrocytes from mouse brain (27). However, as described at the beginning of the article, GDNF and TNF- α as anti-addictive factors cannot be used directly as therapeutic tools for drug dependence. Therefore, we hypothesized that a low molecular weight compound that can induce production of GDNF and TNF- α in the brain would be useful as a novel therapeutic agent for drug dependence. We investigated whether certain

hydrophobic dipeptides, Leu-Ile, Leu-Pro, and Pro-Ile, that partially resemble the immunophilin-binding site on FK506 have neuroprotective effects both in vivo and in vitro attributable to the induction of GDNF (28). Nitta et al. have demonstrated that only Leu-Ile induces GDNF, but not Leu-Pro and Pro-Ile (28). Leu-Ile upregulates GDNF expression by activating heat shock protein 90 / Akt / cyclic adenosine 3',5'-monophosphate response element binding protein signaling (29). Leu-Ile induces TNF- α mRNA in the NAc (10), although the mechanism underlying the upregulation of TNF- α induced by Leu-Ile remains to be elucidated. Taken together, Leu-Ile is expected to induce the production of not only GDNF but also TNF- α and to inhibit drug dependence.

The levels of GDNF mRNA, GDNF, and TNF- α protein are significantly increased 24 h after addition of Leu-Ile compared with those in the control group in primary cultured hippocampal neurons (30). In vivo, Leu-Ile treatment not only in combination with METH, but also after withdrawal from repeated treatment with METH increases GDNF and TNF- α levels in the NAc of mice (30). GDNF is expressed in the neuronal and astroglial cells of the NAc after the repeated co-administration of Leu-Ile and METH, whereas TNF- α is expressed in the neurons in mouse brain (30).

Leu-Ile treatment, in combination with METH and after withdrawal from repeated treatment with METH, inhibits place preference and locomotor sensitization to METH. GDNF and TNF- α are involved in the inhibitory effects of Leu-Ile on the rewarding effects of METH because no effects of Leu-Ile are observed in the GDNF heterozygous and TNF- α knockout mice (30).

To explore the mechanisms of the inhibitory effects of Leu-Ile on METH-induced rewarding effects and locomotor sensitization, the effects of Leu-Ile on the increase in extracellular DA levels and the decrease in DA uptake into synaptosomes induced by repeated METH treatment are examined by using in vivo microdialysis and the [3 H]DA uptake assay, respectively. Leu-Ile inhibits the repeated METH treatment-induced increase in extracellular DA levels in the NAc and negates the METH-induced inhibition of DA uptake in the midbrain. These findings suggest that Leu-Ile inhibits METH-induced rewarding effects and locomotor sensitization by regulating extracellular DA levels via the induction of GDNF and TNF- α expressions (30) (Table 2).

Effects of Leu-Ile, an inducer for GDNF and TNF- α , on MOR-induced dependence

Leu-Ile potentiates the MOR-induced increase in GDNF levels in the NAc of mice (31). Moreover,

Table 2. Summary of the effects of Leu-Ile on methamphetamine- or morphine-induced changes in biomarkers and behavior

	Methamphetamine	Morphine
GDNF levels		
Vehicle	↑	↑
Leu-Ile	↑↑	↑↑
TNF- α levels		
Vehicle	↑	↑
Leu-Ile	↑↑	↑↑
Conditioned place preference		
Vehicle	↑	↑
Leu-Ile	↓	↓
Hyperlocomotion (Single)		
Vehicle	↑	↑
Leu-Ile	↑	↑
Locomotor sensitization (Repeated)		
Vehicle	↑	↑
Leu-Ile	↓	↓
Extracellular dopamine levels		
Vehicle	↑	↑
Leu-Ile	↓	↓

↑, Significant increase; ↓, Significant decrease.

Leu-Ile treatment, in combination with MOR and after withdrawal from repeated treatment with MOR, also increases TNF- α levels in the neuronal cells of the NAc (10).

The effects of Leu-Ile on the MOR-induced rewarding effects and locomotor sensitization are examined in the CPP paradigm and locomotor activity test, respectively. Leu-Ile treatment, in combination with MOR and after withdrawal from repeated treatment with MOR, inhibits place preference and locomotor sensitization to MOR. GDNF and TNF- α are involved in the inhibitory effects of Leu-Ile on the rewarding effects of MOR, because no effects of Leu-Ile are observed in the GDNF heterozygous and TNF- α knockout mice (10, 31).

To explore the mechanisms of the inhibitory effects of Leu-Ile on MOR-induced rewarding effects and locomotor sensitization, the effects of Leu-Ile on the increase in extracellular DA levels induced by repeated MOR treatment are examined by using in vivo microdialysis. Leu-Ile inhibits the repeated MOR treatment-induced increase in extracellular DA levels in the NAc (10). These findings suggest that Leu-Ile inhibits MOR-induced rewarding effects and locomotor sensitization by regulating extracellular DA levels via the induction of GDNF and TNF- α expression (10, 31) (Table 2).

Conclusions

GDNF and TNF- α play important roles in the rewarding effects of both METH and MOR (8–10) (Table 2). Since the deletion of GDNF or TNF- α genes results in an enhancement of the rewarding effects, these cytokines may reduce the rewards of METH and MOR (8–10) (Table 1). As reviewed in this article, some cytokines like GDNF and TNF- α act as anti-addictive factors, whereas others such as tissue plasminogen activator (tPA), metalloproteinase (MMP)-2, MMP-9, basic fibroblast growth factor, neurotrophin-3, and brain-derived neurotrophic factor (BDNF) act as pro-addictive factors (32–34). The tPA-plasmin system, for instance, potentiates the rewarding and locomotor-stimulating effects of METH, MOR, and nicotine by regulating release of DA (34–36). MMP-2 or -9-deficient mice show reduced responses to METH in locomotor sensitization, CPP, and dopamine release in the NAc (33). Infusion of BDNF into the NAc enhances the stimulation of locomotor activity by cocaine in rats, whereas the development of sensitization and CPP is delayed in heterozygous BDNF knockout mice compared with their wild-type littermates (37, 38). The balance of levels between anti-addictive and pro-addictive factors induced by drugs of abuse seems to be important to the development of drug dependence (32). We propose that the dynamic changes and balance of levels in anti-addictive and pro-addictive factors in the brain are some of the determinants of the susceptibility to drug dependence.

As described at the beginning of the article, GDNF and TNF- α as anti-addictive factors cannot be used directly as therapeutic tools for drug dependence. In this article, we demonstrated that Leu-Ile, a low molecular weight compound that induces production of GDNF and TNF- α in the brain, inhibits both METH- and MOR-induced rewarding effects and locomotor sensitization by regulating extracellular DA levels via the induction of GDNF and TNF- α expression (10, 30, 31) (Table 2). Therefore, Leu-Ile could be a novel therapeutic agent for METH- and MOR-induced dependence.

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