

Psychostimulants, Brain Membrane Lipids and Dopamine Transmission

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Abstract

Membrane lipids in the brain play important roles in regulation of the membrane compartmentalization, function and signaling of neurotransmitter transporters and receptors. This review summarizes findings on changes in the composition and metabolism of brain membrane lipids such as phospholipids, cholesterol and sphingolipids following chronic exposure to psychostimulants. We also discussed the mechanisms by which membrane lipids regulate the membrane compartmentalization and function of dopamine transporters and receptors in animal brain tissues and cultured cell lines. This review indicates that chronic psychostimulant exposure causes the remodeling of brain membrane lipids, which may contribute to psychostimulant-induced functional alterations in dopamine transporters and receptors. Brain membrane lipids could be exploited as a new avenue for pharmacological interventions of abnormal brain dopamine transmission and dopamine-related addiction behavior.

Keywords: Brain membrane lipids; Lipid rafts; Psychostimulants; Dopamine transporters; Dopamine receptors

Introduction

Chronic abuse of psychostimulants remains a severe problem across the world, inflicting extensive physical, emotional and economic harm; however, there are still no effective treatments to date. Thus, there is an urgent need to better understand the brain mechanisms that underlie addiction so that new targets can be developed.

Chronic abuse of psychoactive drugs produces profound changes in neurotransmitter transporters and receptors, which have been associated with manifestations of many addiction phenotypes such as tolerance/sensitization, dependence and withdrawal (see reviews in [1]). Although the molecular mechanisms underlying psychostimulant-induced changes in transporters and receptors remain elusive, emerging evidence implicates brain lipids as potential mediators [2]. This review aims to provide a current understanding of the association between chronic psychostimulant exposure and brain membrane lipid profile and highlight the potential contribution of dysregulated brain membrane lipids to altered neurotransmission and associated addiction behavior. The impact of psychostimulant exposure on membrane phospholipid-derived intracellular lipid signaling was extensively reviewed elsewhere [3].

Brain Membrane Lipids and Lipid Rafts

The brain is the most lipid-rich organ in the human body [4]. The three major types of membrane lipids in the brain are phospholipids (e.g. glycerophospholipids), sphingolipids and cholesterol. Glycerophospholipids are glycerol-based phospholipids and a key structural component of the membrane. The brain contains many subtypes of glycerophospholipids including phosphatidylcholine, plasmalogens, phosphatidylserine, phosphatidylinositol, and phosphatidylethanolamine. Sphingolipids, another major lipid found in the plasma membrane, are synthesized from ceramide. The attachment of phosphocholine or saccharides to the hydroxyl group of ceramide leads to the production of sphingomyelin and glycosphingolipids. Gangliosides are glycosphingolipids with terminal sialic acids and are abundant in the brain. Cholesterol, a binding partner of sphingolipids, is a key sterol lipid and accounts for approximately 25% of all lipids in the brain [5]. The composition of these lipids is brain region- and cell type-dependent [6].

The cellular membrane is made of a lipid bilayer which is primarily composed of amphiphilic phospholipids. The lipid bilayer forms a physical barrier that separates the intracellular and extracellular environment. Additionally, sphingolipids and cholesterol form lipid rafts via hydrophobic interactions within the membrane (Figure 1). Lipid rafts are less fluid, when compared with the liquid crystalline phospholipid bilayer, and play a key role in organizing signaling molecules in the membrane to enhance or inhibit signaling events. Many G protein-coupled receptors (GPCRs) and associated signaling proteins are localized in cholesterol-enriched lipid raft microdomains [7]. Cholesterol within lipid rafts can interact with transmembrane proteins such as neurotransmitter receptors, transporters and ion channels. Thus, changes in the composition of the lipid rafts may therefore directly affect receptor compartmentalization, function, signaling and affinity for ligands.

The lipid composition of the membrane can be altered under various conditions such as stress, depression and anxiety via impaired lipid synthesis and metabolism [8]. Dysregulation of membrane lipid metabolism has been associated with a wide spectrum of neurological and psychiatric disorders including Alzheimer's disease, schizophrenia, Parkinson's disease and bipolar disorders [9-11]. This review focuses on abnormal membrane lipid profiles associated with chronic psychostimulant exposure, providing additional evidence to support the notion that brain lipids have an important function in neurotransmission.

Psychostimulants and Brain Membrane Lipid Profile

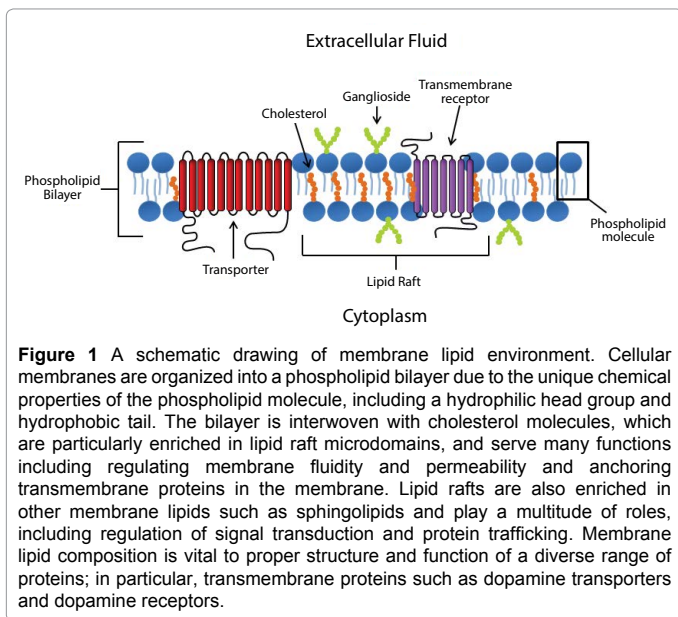
Psychostimulants, such as cocaine and methamphetamine, are highly addictive and widely abused drugs. Cocaine increases the

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extracellular levels of monoamines by blocking reuptake of dopamine, norepinephrine and serotonin through dopamine transporter (DAT), norepinephrine transporter (NET) and serotonin transporter (SERT), respectively. Treatment with methamphetamine, a substrate to DAT, NET and SERT, causes an accumulation of extracellular monoamines primarily via reverse transport of dopamine, norepinephrine and serotonin. The addictive property of psychostimulants is believed to be primarily associated with increased synaptic dopamine activity via acting on DAT [12]. Enhanced dopamine activity induced by cocaine or methamphetamine treatment results in altered membrane localization and function of DAT and dopamine receptors, which are associated with abnormal dopamine transmission and addiction behavior (see review in [13]). Although the mechanisms underlying psychostimulant-induced dysregulation of dopamine transporters and receptors remain elusive, scant evidence implicates the involvement of brain membrane lipids. Since brain membrane lipids play an integral role in membrane protein stability, signaling and function, alterations in membrane lipid composition likely induce functional changes to dopamine transporters/receptors and addiction behavior. Thus, it is important to understand the effects of psychostimulant exposure on membrane lipids in the brain.

Phospholipids

In the brain, phospholipids are the most abundant lipids [14]. Phospholipids comprise various molecular species with different fatty acid moieties in a brain region-dependent manner [15,16]. Chronic exposure to cocaine or methamphetamine has been shown to alter membrane phospholipid metabolism in a brain region-dependent manner. For example, repeated, intermittent injections of cocaine (10-15 mg/kg, i.p.) to male Sprague Dawley rats induce locomotor sensitization, which paralleled changes in brain phospholipids one week after the last cocaine injection [2]. Specifically, cocaine exposure increased phospholipid levels in the hippocampus and the ventral striatum. In contrast, cocaine reduced phospholipid levels in the cerebellum. Furthermore, cocaine-dependent poly drug abusers show reduced levels of phospholipids (e.g. phosphomonoester and phosphodiester) in the central white matter when compared to drug naïve controls [17]. Additionally, concurrent cocaine and heroin

abusers show an increase in cerebral phosphomonoesters when compared to normal controls and no change in phosphodiesters [18]. The altered phospholipid metabolism likely resulted from the changes in the activity of brain phospholipid metabolic enzymes following psychostimulant exposure. Reduced activity of calcium-stimulated phospholipase A2 (cPLA2) was reported in the striatum of human cocaine and methamphetamine users [19,20]. The reduced activity of cPLA2 may be associated with over-stimulation of striatal dopamine receptors because dopamine D2 receptors stimulate cPLA2 activity in CH101 cells [21]. Moreover, the activity of phosphocholine cytidyltransferase, the rate-limiting enzyme of phosphatidylcholine synthesis, is also reduced in cocaine users [20]. Although the biological significance of each phospholipid species is largely unclear, it has been suggested that the cellular localization of phospholipid species is necessary for functional compartmentalization of the plasma membrane of neurons.

For example, reduced expression of 1-oleoyl-2-palmitoyl-phosphatidylcholine, a species of phospholipids and enriched at the protrusion tips of PC12 cells and presynaptic area of mouse neuronal synapses, abolishes the segregation of DAT and Gao proteins to the tip membrane [22]. Future studies should focus on understanding the significance of altered phospholipid species by psychostimulants in dopamine signaling. It is worth noting that phospholipids are abundant in the cortex and plays a critical role in cognition [14]. Thus, alterations in cortical membrane lipids may also be associated with cognition deficits in drug addicts.

Cholesterol

Brain cholesterol content can be altered by drugs of abuse. For example, chronic alcohol exposure increases membrane cholesterol content in whole guinea pig brain or rat cerebellar granule cultured cells [23,24]. However, the effect of psychostimulants on brain cholesterol content has yet to be directly measured. There is only one report on methylphenidate-mediated change in brain cholesterol level [25]. In this study, a single injection of methylphenidate to male Swiss mice reduced [2-3H] acetate (a sterol precursor) incorporation into brain cholesterol during the 24-hr period examined, suggesting that the pharmacological action of methylphenidate may involve lowering cholesterol content in the brain. Additionally, lower circulating cholesterol level was reported to be associated with cocaine relapse in a study of non-opiate and non-alcohol-dependent cocaine addicts, whose cholesterol levels had been determined once during their stay on an inpatient unit [26]. In this study, individuals with lower levels of circulating cholesterol had a significantly greater incidence of relapse 3 months, 6 months, and 1 year after discharge than those of patients who had higher levels of circulating cholesterol. Therefore, it is important to investigate the brain cholesterol content and metabolism following psychostimulant exposure, which may provide new avenues for pharmacological intervention of psychostimulant addiction.

Sphingolipids and gangliosides

Sphingolipids constitute a large class of lipids characterized by their eighteen carbon amino-alcohol backbones as sphingolipid bases. Modification in sphingolipid bases gives rise to diverse structure and function of sphingolipids. Although sphingolipids are not abundant compared to other membrane lipids in the brain, sphingolipids form lipid rafts with cholesterol within the membrane and play an important role in assembling GPCR signaling complex. The most abundant species of sphingolipids in mammalian cells is sphingomyelin [27]. Although there is no report of the effects of psychostimulants on sphingomyelin

in vivo, a study using cultured Rat-1 fibroblasts indicates that cocaine treatment (250-500 μ M, 2-3 days) increases the content of sphingomyelin by abolishing sphingomyelinase activity [28], suggesting that cocaine modulates sphingomyelin content by regulating its metabolism. Additionally, limited data have shown alterations in brain gangliosides, a group of glycosphingolipids. For example, rat offspring exposed to cocaine *in utero* show elevated levels of total gangliosides and glycosphingolipids [29]. Moreover, chronic amphetamine treatment (IP, 20 days) modulates the ganglioside profile of rat frontal cortex, in which the level of quadrisialoganglioside is increased whereas GD1, GM2 and GM3 are decreased [30]. Importantly, altered membrane lipids are associated with cocaine and methamphetamine-induced behavior. For instance, repeated treatment with GM1 (30 mg/kg, IP for 7 days) attenuates amphetamine-induced locomotor sensitization in mice [31]. Moreover, pre-treatment with GM1 in rats enhances the rewarding property of cocaine as determined by conditioned place preference [32]. Although GM1 treatment does not alter the function and expression of DAT, it modifies the brain cocaine disposition by increasing brain cocaine levels. It has been shown that the levels of sphingolipids and gangliosides in the hippocampus and cortex are associated with depression and anxiety [8]. Cocaine addicts are often diagnosed with comorbid depression and/or anxiety [33]. Thus, it is imperative to understand the consequence of altered sphingolipids and gangliosides on neurotransmission and associated behavioral manifestations.

Psychostimulants, Lipid Rafts and Dopamine Transporters/Receptors

Membrane lipid rafts are enriched in cholesterol and glycosphingolipids. The tight interaction between these lipids results in less fluid and highly ordered membrane structures that are resistant to detergent solubilization and are laterally wider than non-raft regions [34,35]. Membrane rafts not only control the localization of many GPCRs but also contain specific subsets of protein complexes that serve to compartmentalize cellular signaling processes. For example, rafts are associated with internalization and endocytotic cargo delivery [36], regulating the internalization of GPCRs and transporters. Emerging evidence indicates that psychostimulant exposure alters membrane compartmentalization (e.g. lipid rafts) of receptors in animal brains and cultured cells. For instance, repeated cocaine administration (20 mg/kg, i.p.) for seven days induces translocation of dopamine receptors in rat frontal cortex [37]. Moreover, dopamine D1 receptors (D1R) translocate from lipid raft to non-lipid raft and the cytoplasmic fractions of the frontal cortex following cocaine treatment whereas the localization of dopamine D5 receptors (D5R) and dopamine D2 receptors (D2R) were not significantly altered. Although there are no *in vivo* studies on the direct association between altered membrane lipid profile and receptor/transporter function, various studies using *in vitro* manipulations of membrane lipids especially cholesterol have provided compelling evidence of cholesterol-mediated localization, internalization and function of monoamine transporters and receptors. Lipid rafts are commonly disrupted *in vitro* with the treatment of methyl- β -cyclodextrin (M β CD, 2.5-10 mM, 30 min), which desorbs cholesterol from the membrane, or filipin (0.5 mg/ml, 30 min), which complexes with and functionally depletes cholesterol [38,39]. Literature suggests that the integrity of lipid rafts is critical for membrane compartmentalization and function of dopamine transporters and receptors.

Cholesterol content and membrane compartmentalization of dopamine transporters and receptors

DAT compartmentalization in membrane lipid raft and non-raft microdomains has been demonstrated in LLC-PK1 cells, neuroblastoma

N2A cells, and rat striatal tissues fractionated by sucrose density gradient centrifugation [40-42]. Both raft- and non-raft-associated DAT can undergo constitutive internalization in neuroblastoma SK-N-MC cells [43]. Disruption of lipid rafts with M β CD or filipin in LLC-PK₁ cells does not alter the lateral movement of DAT between rafts and non-rafts [40]; however, treatment with M β CD (5 mM) or nystatin (25 μ g/ml, a cholesterol chelator in rafts) in HEK293 cells reduces DAT association with lipid raft microdomain [44]. There are conflicting data on the involvement of cholesterol in DAT internalization mediated by protein kinase C (PKC), a key mechanism of DAT internalization. Raft-associated DAT was shown to be resistant to internalization upon treatment with PKC, which is in contrast to non-raft-associated DAT in LLC-PK₁ cells [40]. However, in SK-N-MC cells, PKC-stimulated DAT internalization primarily occurs in membrane raft microdomains [43]. The variations in cell lines and experimental techniques of these experiments may contribute to the discrepancy.

The regulation of DAT localization by membrane lipids is further supported by the formation of complexes between DAT and membrane raft-associated proteins. For example, flotillin-1 and DAT can be co-immunoprecipitated in HEK293 cells [45,46]. DAT and flotillin partition in similar detergent-resistant membrane fractions [41,45] and depletion of flotillin shifts DAT localization to non-rafts [45]. Flotillin facilitates PKC-mediated DAT internalization in HEK293 cells [45]; however, it was also reported that flotillin knockdown via siRNA does not alter PKC-mediated DAT trafficking [46]. Additionally, DAT physically interacts with Rin, a Ras-like GTPase, and they form a complex in lipid raft microdomains of rat PC12 cells [47]. Disruption of Rin and DAT interaction abolishes PKC-regulated DAT internalization. Thus, DAT interactions with raft-associated proteins dictate the localization and/or internalization of DAT.

Membrane localization of dopamine receptors such as D1R and D2R is also mediated by membrane lipid composition (see review in [48]). D1Rs are primarily localized in lipid raft microdomains in HEK293 and COS-7 cells and can physically interact with caveolae, a raft-associated protein [49,50]. D1Rs and caveolae can form a functional complex in lipid rafts and regulate D1R-mediated G protein signaling. Similar to D1Rs, D2Rs are also primarily localized in lipid raft microdomains in HEK293 cells and mouse striatum tissues [51,52] although it is unknown whether D2Rs physically interact with certain raft-associated proteins. Moreover, dopamine-induced D2R internalization is largely restricted to D2Rs localized in lipid rafts [53]. Together, these data support the notion that the specialized compartmentalization of receptors/transporters in the lipid microdomains determines their internalization rate.

Cholesterol content and the function of transporters/receptors

The localization of transporters/receptors in the lipid microdomains has functional significance. For instance, exogenously increasing membrane cholesterol level in striatal synaptosomes and neuronal-like MN9D cells increases the binding B_{max} values for cocaine analogs but had no effect of DAT surface level [51]. Moreover, cholesterol depletion with M β CD significantly reduced the ability of DAT to take up dopamine without altering DAT surface expression in LLC-PK₁, HEK293 and N2A cells [40,41,44]. Furthermore, cholesterol depletion with M β CD attenuates the ability of DAT to reverse transport dopamine in HEK293 and N2A cells [41,44]. Accordingly, knockdown of DAT-associated flotillin-1 proteins results in attenuation of amphetamine efflux in primary mesencephalic dopaminergic neurons, further demonstrating the importance of lipid raft localization in DAT function.

Dopamine receptor function is also mediated by membrane lipid composition. For instance, D1R and D2R binding activity is primarily concentrated in the raft fractions of rat striatal membranes [52]. Additionally, the maximum number of D1R binding sites for SCH23390 in bovine caudate synaptosomes is insensitive to alterations in the ratio of cholesterol and phospholipid [54]. However, when the ratio is increased by 30%, the binding affinity is reduced and the activity of dopamine-stimulated adenylate cyclase is markedly inhibited. In contrast, cholesterol depletion via m β CD treatment increases D1R-mediated cAMP accumulation, which can be reversed upon cholesterol replenishment in COS-7 cells [50]. Moreover, co-expressing human D1R and lipid raft-associated protein caveolin-2 in HEK293 cells increases D1R-mediated adenylyl cyclase activity [49]. These findings suggest brain membrane lipids are key modulators of the membrane compartmentalization, trafficking and function of DAT and dopamine receptors. Dysregulation of brain membrane lipids would impact dopamine transporter/receptor-mediated dopamine transmission and associated addiction behavior.

Therapeutic Potentials of Lipid-modifying Drugs in the Treatment of Psychostimulant Addiction

Lipid-modifying drugs in recent years have been experimented for treatment of various neurological disorders including Alzheimer's disease; Parkinson's disease and stroke (see review in [55]). For example, there is an increasing interest in the therapeutic potential of reducing cholesterol levels in the treatment and prevention of Alzheimer's disease. A clinical trial on patients with mild to moderate Alzheimer's disease indicates that treatment with atorvastatin, a cholesterol lowering drug, produces positive outcomes on Alzheimer's progression after 6 and 12 month evaluation [56]. Moreover, a lower level of circulating cholesterol is associated with reduced production of amyloid beta observed in Alzheimer disease [57]. However, the beneficial effects of cholesterol lowering drugs have not been consistent [58]. Additionally, scant literature suggests that lipid-modifying drugs may be beneficial in the treatment of alcohol and nicotine abuse. For example, intragastric administration of gemfibrozil (50 mg/kg), a cholesterol- and triglyceride-lowering drug, diminishes ethanol intake in male Sprague Dawley rats [59]. Furthermore, treatment with clofibrate (200-300 mg/kg, i.p.), another FDA approved cholesterol- and triglyceride-reducing drug, significantly reduces nicotine-taking behavior and reinstatement in male Sprague Dawley rats with a prior history of nicotine exposure, which parallels clofibrate's ability to block nicotine-induced dopamine release in the nucleus accumbens and neuronal firing in the ventral tegmental area [60]. To date, there is no report on the therapeutics of lipid-modify drug in the treatment of psychostimulant addiction. These lipid-modifying drugs may be beneficial for drug addicts with abnormal lipid profiles.

Conclusion

Membrane lipids in the brain play an important role in regulation of the membrane compartmentalization, internalization and function of neurotransmitter transporters and receptors. This review highlights profound alterations in brain membrane lipids and paralleled changes in the function of dopamine transporters and receptors following chronic exposure to psychostimulants such as cocaine and methamphetamine. To date, it is unknown whether the remodeling of brain membrane lipids contributes to altered localization and function of dopamine transporters and receptors. Given the brain region dependent changes in membrane lipids, it is likely that these changes are associated with different aspects of addiction including

enhanced motivation for drug- seeking and cognitive deficits. Thus, future studies designed to characterize the underlying mechanisms regulating the association between chronic psychostimulant abuse and membrane lipids, with respect to spatial and temporal aspects of dopaminergic neurotransmission, are essential. Brain membrane lipids could be exploited as a new avenue for pharmacological interventions of abnormal brain dopamine transmission and addiction behavior.

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