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Lipids and drugs of abuse

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Abstract

Drug abuse continues to take an enormous economic and social toll on the world. Among the costs are reduced productivity, increased need for medical services and stress on families. Treatments that allow affected individuals to reduce compulsive drug use are lacking and novel approaches to their development will likely come from increased understanding of the consequences of chronic exposure to reinforcing drugs. The purpose of this review is to explore the role of lipids in drug abuse and to present a rationale for an increased focus on the interactions between drugs of abuse and lipids in the brain. Small molecular weight lipids function as neuromodulators in the brain and, as such, play a role in the synaptic plasticity that occurs following exposure to drugs of abuse. In addition, the membrane lipid bilayer consists of lipid subdomains and emerging evidence suggests that protein function can be altered by transient associations with these subdomains. Finally, lipidomics is a very new field devoted to the exploration of changes in cellular lipid constituents during phenotypic alterations. Enhanced research in all of these areas will likely provide useful insights into and, perhaps, therapeutic targets for the treatment of drug abuse.

Keywords: Endocannabinoids; Neuromodulator; Arachidonic acid; Membrane lipid domains

Introduction

The purpose of this review is to explore the role of lipids in drug abuse and to present a rationale for an increased focus on the interactions between drugs of abuse and lipids in the brain. Three topics are developed in this paper. The first is that small molecular weight lipids function as neuromodulators in the brain and, as such, play a role in the synaptic plasticity that occurs following exposure to drugs of abuse.

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The second topic is that membrane bilayer lipid subdomains should be considered as a component of signal transduction processes and possible site of action of drugs of abuse. Finally, the very new field of lipidomics holds promise as a way to get a handle on the composition of cellular lipids with the ultimate goal of determining changes in the lipidome that occur following many stimuli, including exposure to drugs of abuse.

Synaptic changes occur following chronic exposure to drugs of abuse

A common feature of drugs that are abused by humans is that they are reinforcing. A drug is classified as a reinforcer if it enhances the probability of a previously neutral response. For example, in the conditioned place preference paradigm, placing a rat or mouse into a chamber immediately after cocaine administration increases the probability that the animal will go to that chamber when given a choice. During the conditioning phase, a strong association is made between the reinforcing drug and the environment (Wise, 1996). Repeated exposure to reinforcing drugs initiates long-lasting remodeling of brain circuits that are normally used to reinforce rewarding behaviors (i.e. cortico-mesolimbic dopaminergic pathways) and/or circuits involved in learning the behaviors and attaching significance to them (i.e. hippocampus, amygdala and cortex). Not all drugs of abuse have the same mechanism of action, but they share a common ability to produce pathological interruptions of the normal functioning of these key brain circuits.

It is generally believed that the brain adaptations resulting from repeated exposure to reinforcing drugs underlie the disease of human drug addiction (Hyman and Malenka, 2001). These adaptations result in complex changes in behavior, including drug seeking as described above; tolerance to the reinforcing effects of the drug; and alterations in the aversive symptoms associated with drug withdrawal (Nestler, 2004). The modifications produced by reinforcing drugs last far beyond the disappearance of the drug, strongly indicating that durable changes have been induced during exposure to the drug. Therefore, enhanced understanding of the molecular and cellular adaptations of the brain that occur following exposure to drugs of abuse will likely lead to novel approaches for the prevention or treatment of human drug addiction.

Exposure of the brain to reinforcing drugs produces long-lasting derangement of synaptic transmission. Changes in the functional strength of synaptic connections in a mature animal are often referred to as “synaptic plasticity”. There are multiple mechanisms that result in changes in synaptic strength. The effectiveness of synaptic transmission can be altered by events that occur on the presynaptic side, resulting primarily in changes in the amount of neurotransmitter synthesized and/or released. Alternatively, the postsynaptic side of the synapse can become more or less sensitive to the actions of neurotransmitter binding to its receptor(s). Changes in the number of cell surface receptors results in altered effectiveness of signaling as do changes in phosphorylation state of receptors, particularly ion channel-linked receptors, and downstream signaling molecules.

There are many studies demonstrating that exposure to reinforcing drugs results in synaptic plasticity in several brain regions (see (Gerdeman et al., 2003; Kauer, 2004; Nestler, 2004) for excellent reviews of this topic). Current data strongly suggest that reinforcing drugs modulate long-term depression (LTD) and long-term potentiation (LTP), processes that are critically important for learning and memory, in a manner that results in pathological changes in neuronal circuitry, particularly in the limbic system. Data, discussed more fully below, indicate that small molecular weight lipids are mediators of synaptic