Journal of Chemical Neuroanatomy xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Chemical Neuroanatomy

journal homepage: www.elsevier.com/locate/jchemneu

Tamoxifen and amphetamine abuse: Are there therapeutic possibilities?

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ARTICLE INFO

Article history:
Received 4 May 2016
Received in revised form 5 August 2016
Accepted 14 August 2016
Available online xxx

Keywords:
Tamoxifen
Amphetamine
Dopamine
Protein kinase C
Bipolar mania

ABSTRACT

Although best known as a selective estrogen receptor modulator (SERM), tamoxifen is a drug with a wide range of activities. Tamoxifen has demonstrated some efficacy has a therapeutic for bipolar mania and is believed to exert these effects through inhibition of protein kinase C (PKC). As the symptoms of amphetamine treatment in rodents are believed to mimic the symptoms of a manic episode, many of the preclinical studies for this indication have demonstrated that tamoxifen inhibits amphetamine action. The amphetamine-induced increase in extracellular dopamine which gives rise to the 'manic' effects is due to interaction of amphetamine with the dopamine transporter. We and others have demonstrated that PKC reduces amphetamine-induced reverse transport through the dopamine transporter. In this review, we will outline the actions of tamoxifen as a SERM and further detail another known action of tamoxifen—inhibition of PKC. We will summarize the literature showing how tamoxifen affects amphetamine action. Finally, we will present our hypothesis that tamoxifen, or an analog, could be used therapeutically to reduce amphetamine abuse in addition to treating mania.

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1. Introduction

Nearly all addicting drugs, and notably amphetamine, increase dopamine in the nucleus accumbens. Deletion of dopamine or blockade of dopamine receptors abolishes self-administration of addictive drugs and electrical stimulation of dopamine neurons maintains brain stimulation reward (Xi and Gardner, 2008). The reinforcing properties of amphetamine depend on the enhanced levels of extracellular dopamine (Ranaldi et al., 1999), elicited by amphetamine binding to the dopamine transporter (Sulzer et al., 2005). If tamoxifen has utility for treatment of bipolar mania, it might also have a deterrent effect on amphetamine abuse. There is, at present, no therapeutic approved for the treatment of amphetamine use disorder and there is a huge unmet need. In 2013, the number of individual amphetamine-type stimulants

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http://dx.doi.org/10.1016/j.jchemneu.2016.08.004
0891-0618/

reported to the United Nations Office of Drug Control reached 348, up from 251 in 2012. Methamphetamine is a markedly destructive drug that has been abused by >13,000,000 people, but recent abuse of the related prescription drug, Adderall® (amphetamine), is escalating (Brandt et al., 2014) as is use of cathinones, known as β-ketone-amphetamines or "bath salts" (Prosser and Nelson, 2012). Suicide as a risk of amphetamine dependence accounted for 854,000 drug abuse life years in the Global Burden of Disease Study 2010 (Degenhardt et al., 2013). Numerous drugs to treat this disorder have been tested in clinical trials: indirect dopamine agonists (low-dose amphetamine and modafinil), and partial agonists (aripiprazole), opioid antagonist (naltrexone), serotonin/norepinephrine reuptake inhibitors and, recently topiramate and bupropion. No single drug or drug combination has shown consistent efficacy in therapeutic trials for amphetamine use disorder (Brackins et al., 2011; Brensilver et al., 2013; Carson and Taylor, 2014; Heinzerling et al., 2014; Ling et al., 2012).

As a substrate of the dopamine and norepinephrine transporters, amphetamine blocks uptake of these catecholamines by the transporters and subsequently elicits a reversal of transport to release the catecholamines into the extracellular space (Sulzer et al., 2005). The increase in extracellular dopamine is the main mechanism by which amphetamine elicits hyperactivity in man and laboratory animals (Wise and Bozarth, 1987). The discovery that tamoxifen was useful as a therapeutic for bipolar mania (Bebchuk et al., 2000) led to the preclinical finding that tamoxifen would block hyperactive behaviors elicited by amphetamine in male rats, because amphetamine hyperactivity is a model for mania in laboratory animals (Einat et al., 2007). It is postulated that this action of tamoxifen is due to its ability to block protein kinase C (PKC), as opposed to its estrogen receptor binding activity. This hypothesis (Zarate and Manji, 2009) has merit due to the reported inhibition of amphetamine-stimulated dopamine efflux by inhibitors of PKC by our lab and others (Giambalvo, 1992; Gnegy, 2003). We posit that by knowing how tamoxifen works in the brain and affects the dopaminergic system, whether it is via PKC, binding to the estrogen receptor, or another previously undescribed mechanism, novel therapeutics may be created to prevent amphetamine abuse without causing serious adverse events.

We have long suggested that a PKC inhibitor may have potential as a therapeutic for amphetamine abuse. Though multiple PKC inhibitors have gone to clinical trials, with varying degrees of success, tamoxifen is the only PKC inhibitor exhibiting any kinase specificity that is capable of crossing the blood-brain barrier (Chico et al., 2009). The drug tamoxifen has a multiplicity of reported actions beyond its original clinical indication as an estrogen receptor modulator, including inhibition of PKC. Because of our interest in PKC inhibitors as a therapeutic for amphetamine abuse, here we present a review of the body of work which indicates a new potential therapeutic role for the old drug, tamoxifen.

2. Tamoxifen

Tamoxifen is a first generation non-steroidal selective estrogen receptor modulator (SERM) and is primarily used as the standard of care for the treatment and prevention of recurrence in pre- and post-menopausal women with estrogen receptor-positive breast cancer (Early Breast Cancer Trialists' Collaborative et al., 2011). In the United States, tamoxifen was the first anti-estrogen medication approved for clinical use to prevent and reduce breast cancer occurrence (Jordan, 2003). Tamoxifen was initially referred to as an anti-estrogen as it blocks estrogen receptors in breast tissue, thus reducing effects caused by estrogen. However, tamoxifen also acts as an agonist at estrogen receptors in certain regions of the body such as the endometrium, liver, and bone; thus, its reclassification as a SERM. Tamoxifen also mimics the effect of estrogen in assessment of cardiovascular tone (Leung et al., 2007). Similarly, the drug raloxifene is estrogenic in bone tissue while being antiestrogenic in breast tissue, and as such has proven useful as a preventative treatment for osteoporosis in post-menopausal women, but which lacks the increased cancer risk and other unpleasant side effects of hormone replacement therapy (Dane et al., 2007; Pinkerton and Thomas, 2014). Tamoxifen is generally taken for five years followed by a different therapeutic depending on the patient's condition. Recent results from the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial concluded that ten years of adjuvant tamoxifen therapy reduce mortality to a greater extent than five years (Davies et al., 2013). As such, it is important to consider the long-term effects of tamoxifen on CNS function.

Tamoxifen is a lipophilic compound that accumulates in tissue, including brain, (Lien et al., 1991a) giving it a high apparent volume of distribution of 50–60 liters (Lien et al., 1989). Despite the observation that tamoxifen and its metabolites are substrates for P-glycoprotein (Iusuf et al., 2011), tamoxifen readily crosses the blood brain barrier and concentrations in brain tissue can reach levels 40 times higher than concentrations in serum (Lien et al., 1991b). The elimination half-life of tamoxifen in humans ranges from 7 to 10 days (de Vos et al., 1992). There are three known active metabolites: N-desmethyltamoxifen, 4-hydroxytamoxifen, and 4-hydroxy-N-desmethyltamoxifen, also known as endoxifen (Fig. 1A). N-desmethyltamoxifen is the primary metabolite in humans, followed by endoxifen and then 4-hydroxytamoxifen. N-desmethyltamoxifen circulates at concentrations 2–3 fold higher than tamoxifen but is equipotent to tamoxifen at the estrogen receptor (Lien et al., 1991a). Both hydroxylated metabolites are 100-fold more active than tamoxifen and have activity at the estrogen receptor commensurate with estradiol (Furr and Jordan, 1984; Leung et al., 2007). Thus, tamoxifen is considered to be a prodrug. The microsomal enzyme CYP2D6 is responsible for the metabolism of tamoxifen to both 4-hydroxytamoxifen and endoxifen, such that drug–drug interactions are a consideration in patients taking tamoxifen (Jordan, 2007).

As mentioned above, tamoxifen can cross the blood brain barrier, yet its activity in the brain is not fully understood, nor has it been clearly delineated as an estrogen receptor agonist or antagonist in the relevant cells. Some studies have demonstrated agonist effects of tamoxifen in the CNS, particularly at G-protein coupled estrogen receptors (Gibbs et al., 2014). In contrast, recent research has led to the assumption that tamoxifen acts as an antagonist in the brain due to its opposite effect on cognition as estrogen (Chen et al., 2014). In order to properly understand the context of our investigation into the dopamine-modulating effects of tamoxifen, we must first explore the mechanisms of action of the drug. The first to be discussed is its role as an estrogen receptor modulator especially since estrogen itself has notable effects on the dopaminergic system.

3. Neurological effects of estrogen

Classified as the main female sex hormone, estrogen (17-β-estradiol) is involved in the growth of female sex organs, the distribution of body fat, and the regulation of various behaviors. In the central nervous system, estrogen improves cognition and improves memory, while offering protection against various neurotoxic insults (Engler-Chiurazzi et al., 2016).

Estrogen receptors have two forms, ERα and ERβ, encoded by separate genes. Classically, estrogen exerts its effects by stimulating the translocation of estrogen receptors α or β into the nucleus where the receptors affect the expression of numerous genes. More recently, it has become clear that estrogen exerts a number of rapid, non-genomic effects, both through the classical estrogen receptors, which can translocate to the membrane to interact with

Please cite this article in press as: S. Mikelman, et al., Tamoxifen and amphetamine abuse: Are there therapeutic possibilities?, J. Chem. Neuroanat. (2016), http://dx.doi.org/10.1016/j.jchemneu.2016.08.004