Nuclear peroxisome proliferator activated receptor-gamma (PPARγ) as a therapeutic target to treat neurodegeneration and dependence elicited by drugs of abuse

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Peroxisome proliferator activated receptors (PPARs) are ligand-activated transcription factors that are located in the cytoplasm. After activation by specific ligands, PPARs enter the nucleus and heterodimerize with the retinoid X receptor. This heterodimer binds to PPAR response element in DNA to regulate the transcription of genes that are involved in different physiological processes, including insulin sensitization, inflammatory response, and neuroprotection (Kapadia et al., 2008). The PPAR receptor family is composed of three isoforms—PPARα, PPARδ and PPARγ—that are expressed in both peripheral tissues and the brain. Endogenous ligands of PPARγ include polyunsaturated fatty acids (e.g., oleic acid and arachidonic acid), prostaglandins, and low-density lipoproteins. PPARγ can also be targeted by specific synthetic agonists that belong to the class of thiazolidinediones (TZDs), including pioglitazone and rosiglitazone. Because of their ability to bind PPAR, TZDs are approved for the treatment of type 2 diabetes and insulin resistance, improving insulin sensitivity in muscle, liver, and adipose tissue.

High to moderate PPARγ expression has been detected in several brain regions, including the ventral tegmental area, nucleus accumbens, amygdala, and hippocampus (Moreno et al., 2004), that are known to play a role in the modulation of reward mechanisms, mood, and learning (Figure 1A). Consistent with the brain distribution of PPARγ, accumulating evidence links this receptor to drug addiction and mood disorders, and TZDs have been proposed for the treatment of these pathologies. For example, we found that the oral administration of pioglitazone and rosiglitazone reduced alcohol self-administration in rats. This effect of TZDs was blocked by pretreatment with the PPARγ antagonist GW9662. Furthermore, pioglitazone markedly reduced the reinstatement of alcohol seeking that was elicited by stress but not by environmental cues and mitigated negative symptoms that are typically associated with alcohol withdrawal (Stopponi et al., 2011). The effects of PPARγ agonists occur independently of their insulin-sensitizing properties and are mediated by PPARγ activation in the brain (Stopponi et al., 2011). In rodent studies, we demonstrated the possibility of targeting PPARγ for the treatment of opioid abuse. The activation of PPARγ by pioglitazone reduced the motivation to self-administer heroin, prevented the stress-induced reinstatement of drug seeking, and attenuated the expression of negative symptoms of opioid withdrawal (de Guglielmo et al., 2017). Electrophysiological and microdialysis studies demonstrated that PPARγ activation attenuates the ability of drugs of abuse to stimulate dopaminergic neurons in the ventral tegmental area, thereby attenuating dopamine release in the nucleus accumbens (de Guglielmo et al., 2015). This is currently considered the primary mechanism by which TDZs reduce the motivation for drugs of abuse. Notably, although pioglitazone did not influence the cue-induced reinstatement of alcohol or heroin seeking, it has been recently reported that its efficacy against cue-induced relapse in rats that self-administered cocaine (Stopponi et al., 2011; de Guglielmo et al., 2015; Miller et al., 2018). To date, some small clinical trials have been conducted to evaluate the therapeutic effects of pioglitazone in opioid abusers. These studies reported a reduction of craving for drugs of abuse, whereas no effects on drug “liking” were detected (Jones et al., 2018). Another small clinical study evaluated the effect of pioglitazone on opioid withdrawal symptoms during buprenorphine taper in dependent patients, but no evidence of efficacy was observed (Schoeder et al., 2018). PPARγ agonists have marked anti-inflammatory actions. Rodent studies found that pioglitazone exerts powerful neuroprotective effects against neuronal insult that is elicited by exposure to high-dose alcohol (Cipitieli et al., 2017). The neuroprotective properties of this drug were confirmed in a recent clinical study in cocaine-dependent patients, in which a few weeks of pioglitazone treatment reduced drug craving and improved white matter integrity in the brain (Schmitz et al., 2018). Clinical and preclinical evidence highlights a possible role for PPARγ in affective disorders, including depression, anxiety, and bipolar disorder, that are often linked to drug addiction. For example, in mice with the genetic deletion of PPARγ, we found that the constitutive knockdown of this receptor enhanced basal anxiety-like behavior and sociability (Jones et al., 2016). The link between nicotine abuse and the amygdala and the hippocampus (Domi et al., 2016, 2019) points to a more generalized role of this nuclear receptor in the modulation of brain GABA transmission.

Anxiety, irritability, and weight gain that emerge during nicotine withdrawal contribute to the resumption of smoking in patients who attempt to quit. A tempting speculation is that PPARγ agonist treatment may mitigate negative symptoms that are associated with nicotine withdrawal and thus facilitate successful smoking cessation. A recent study examined the link between nicotine abuse and diabetes. Chronic nicotine intake enhanced circulating levels of glucagon and insulin, altered glucose homeostasis, and resulted in the emergence of signs of diabetes in mice (Duncan et al., 2019). The link between nicotine abuse and the development of insulin resistance has also been reported in clinical studies. PPARγ agonists may be an important treatment aid for type 2 diabetes patients who experience difficulty in quitting smoking. A recent study of nicotine-dependent patients reported promising results that showed that pioglitazone reduced drug craving, but no effect on drug liking was detected (Jones et al., 2018). Future perspectives on PPARγ as a target for the treatment of drug abuse (and a major limitation in the use of pioglitazone for the treatment of drug abuse and related neurological conditions is its relatively low blood-brain barrier permeability. Data from rats, monkeys, and dogs show that pioglitazone is well absorbed in the gastrointestinal tract after oral administration and achieves good exposure levels in peripheral tissues, but only a fraction (~10%) of plasma pioglitazone reaches the brain (Maeshiba et al., 1997). Another T2D, rosiglitazone, which was originally approved for the treatment of type 2 diabetes but later withdrawn from the market in several countries because of cardiovascular toxicity, has an even worse pharmacokinetic profile. For example, only 0.045% of an injected dose per gram of tissue crosses the blood-brain...
barrier after intravenous administration. These data indicate that therapeutic doses of these drugs result in relatively low PPARγ engagement in the brain.

To overcome this limitation, it would be useful to have better brain penetrating PPARγ agonists. Moreover, a significant advantage could come from molecules that, due to their binding properties, recruit specific coactivator or corepressor resulting in the activation of certain intracellular transcription pathways but not others (Govindarajulu et al., 2018).

Despite promising results in laboratory animals, clinical data have not conclusively supported the efficacy of TZDs for the treatment of substance abuse-related neurodegenerative conditions and mood disorders. Another limitation is that few clinical studies that have evaluated the effects of pioglitazone on drug addiction have had small sample sizes, which hampers the ability to capture relatively small effect sizes that likely occur with low brain PPARγ engagement.

Nevertheless, considering the strong evidence of efficacy in preclinical studies and promising results of clinical trials, better efficacy may be achieved by greater PPARγ engagement in the brain. Future studies and innovative research and development efforts should seek to design better brain-penetrant molecules to better test the efficacy of PPARγ agonists for the treatment of drug abuse, neurodegenerative and mood diseases.

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E-Creditors: Zhao M, Li J; E-Editor: Jia Y

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