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. Endogeneous ligands of PPARγ include polyunsatured 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 PPARγ, 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 from 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 (Schroeder 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 (Cippitelli 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., 2017).

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 responsiveness to acute stress. In wildtype littermates, we found that a direct microinjection of pioglitazone in the amygdala, an area where PPARγ colocalizes with γ-aminobutyric acid-ergic cells, prevented the anxiogenic effect of stress (Domi et al., 2016).

In humans, treatment with pioglitazione attenuated the expression of depressive symptoms in bipolar patients and in individuals who suffered from major depressive disorder. Reductions of anxiety symptoms were reported in heroin-dependent subjects who were treated with pioglitazone for a few weeks (Jones et al., 2018). These findings are particularly relevant because negative affective symptoms that are associated with drugs withdrawal have important clinical significance for the prevention of drug seeking and relapse. A current hypothesis under investigation is that these effects of PPARγ agonists on mood disorders and substance abuse are linked to their neuroprotective and anti-inflammatory properties.

We recently published a proof-of-concept study to support the therapeutic potential of pioglitazone for the treatment of negative affective symptoms that are associated with drug withdrawal. In this study, we made mice dependent on nicotine and then treated them with pioglitazone during the expression of acute withdrawal and after protracted abstinence. The results showed that exogenous PPARγ activation attenuated both the expression of somatic signs of withdrawal after the abrupt cessation of nicotine administration and anxiety-like behavior after a period of protracted abstinence (Domi et al., 2019). We also found that a site-specific microinjection of pioglitazone in the amygdala attenuated the heightened expression of anxiety-like behavior that was associated with protracted abstinence, but no effects on somatic symptoms were detected during acute withdrawal. Conversely, a microinjection of pioglitazone in the hippocampus attenuated the expression of somatic symptoms but had no effects on anxiety-like behavior (Domi et al., 2019).

The role of PPARγ in abuse-related behaviour is associated with its ability to modulate the γ-aminobutyric acid (GABA) ergic trasmission. Previous studies showed that pioglitazone, increasing GABA activity in rostromedial tegmental nucleus neurons impinging onto ventral tegmental area dopamine (DA) cells, attenuates their firing rate and, as a consequence, reduces extracellular DA in the Nac (**Figure 1B**). This may represent the primary mechanisms through which activation of PPARγ by pioglitazone attenuates the motivation for heroin and possibly other substances of abuse (de Guglielmo et al., 2015). Emerging data demonstrates that PPARγ is expressed in GABA positive neurons also in other brain regions such as the the amygdala and the hippocampus (Domi et al., 2016, 2019). This 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 consumption 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: One 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 TZD, rosiglitazone, which was originally approved for the treatment of type 2 diabetes but later withdrawn from the market in several countries because of cardiotoxicity, has an even worse pharmacokinetic profile. For example, only 0.045% of an injected dose per gram of tissue crosses the blood-brain

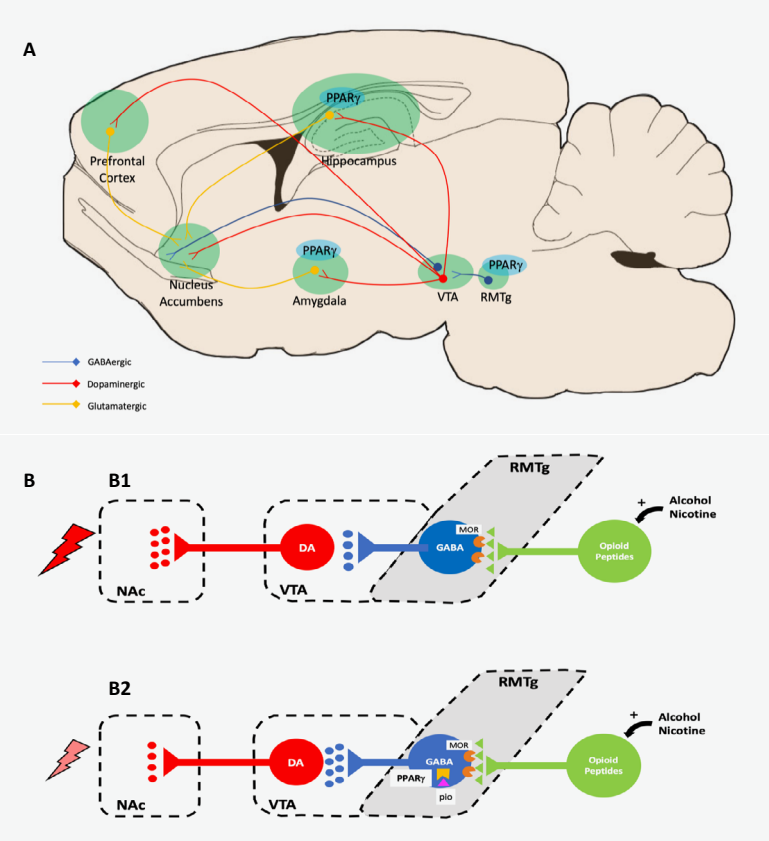

Figure 1 | **PPARγ expression in brain areas linked to addiction-related behaviors.**
(A) Schematic representation that highlights (green) the brain nuclei in which peroxisome proliferator activated receptor-gamma (PPARγ) is expressed. PPARγ is expressed in several areas involved in motivation and emotion. These include the ventral tegmental area (VTA), the rostromedial tegmental nucleus (RMTg), the nucleus accumbes (Nacc), the prefrontal cortex (PFC), the amygdala (AMY) and the hippocampus (HIPP). PPARγ is colocalized with GABAergic cells in the HIPP and in the RMTg and in glutamatergic and γ-aminobutyric acid (GABA)ergic cells in the AMY. (B) Schematic representation of the mechanism through which drugs of abuse can act on RMTg/VTA-NAc circuit and how the modulation of PPARγ can counteract their effect. (B1) Drugs like nicotine and alcohol enhance presynaptic endorphine release with a subsequent decrease GABA transmission in RMTg neurons impinging onto VTA dopamine (DA) cells. This may result in a disinhibited DA transmission and enhanced release of this catecholamine in the NAc. Opioid agonists, through activation of mu-opioid peptide (MOP) receptor in GABA positive cells, can directly attenuate their tonic inhibition on VTA DA neurons; (B2) activation of PPARγ in the RMTg facilitates presynaptic GABA release that, in turn, reduces the ability of drug of abuse to stimulate VTA dopamine neurons.

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 TDZs for the treatment of substance abuse-related neurodegenerative conditions and mood disorders. Another limitation is that the 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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