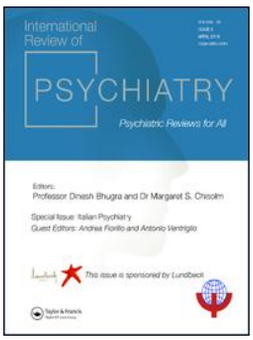

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REVIEW ARTICLE

Psychedelics as anti-inflammatory agents

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ABSTRACT

Serotonin (5-hydroxytryptamine, 5-HT)$_{2A}$ receptor agonists have recently emerged as promising new treatment options for a variety of disorders. The recent success of these agonists, also known as psychedelics, like psilocybin for the treatment of anxiety, depression, obsessive-compulsive disorder (OCD), and addiction, has ushered in a renaissance in the way these compounds are perceived in the medical community and populace at large. One emerging therapeutic area that holds significant promise is their use as anti-inflammatory agents. Activation of 5-HT$_{2A}$ receptors produces potent anti-inflammatory effects in animal models of human inflammatory disorders at sub-behavioural levels. This review discusses the role of the 5-HT$_{2A}$ receptor in the inflammatory response, as well as highlight studies using the 5-HT$_{2A}$ agonist (*R*)-2,5-dimethoxy-4-iodoamphetamine [(*R*)-DOI] to treat inflammation in cellular and animal models. It also examines potential mechanisms by which 5-HT$_{2A}$ agonists produce their therapeutic effects. Overall, psychedelics regulate inflammatory pathways via novel mechanisms, and may represent a new and exciting treatment strategy for several inflammatory disorders.

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Introduction

The term 'psychedelic' was coined in 1957 by Humphrey Osmond for a class of drug that is able to produce profound changes in thought, mood, and perception (Osmond, 1957). This term is now coming to prominence again in the scientific realm to distinguish a specific class of hallucinogenic drugs that exert their primary effects through activation of serotonin 5-HT$_{2A}$ receptors from those that utilize different primary molecular mechanisms for their effects (Nichols, 2016). Results of recent clinical studies using known psychedelic compounds have contributed to a greater appreciation of their potential as therapeutic medications. In two separate human clinical trials performed at Johns Hopkins University and New York University, the effects of psychedelic-assisted psychotherapy in patients suffering from cancer-related psychosocial distress (CRPD) was examined (Griffiths et al., 2016; Ross et al., 2016). Each placebo-controlled double-blind study found that the 5-HT$_{2A}$ receptor agonist psilocybin significantly improves well-being and life satisfaction, while concurrently reducing anxiety and depression in patients with a life-threatening cancer diagnosis. This effect can persist for at least 6 months after a single administration of drug. At about the same time another group, at Imperial College in London, found that psilocybin administration has significant anti-depressant effects. This study, however, was smaller and open label, with no placebo-control group (Carhart-Harris et al., 2016a, 2017a). The Imperial group further utilized imaging techniques (fMRI) to elucidate the effects of psilocybin and LSD on brain network connectivity (Carhart-Harris et al., 2012, 2016b). They found that these drugs alter connectivity between brain regions, especially with regard to the Default Mode Network, to produce a transient hyperconnected state (Carhart-Harris et al., 2017b). As the drug's effects wear off, the brain may reset into a more normal pattern of connectivity that is less associated with previous depressive states.

It is now recognized that inflammation plays a significant role in the pathophysiology underlying psychiatric disorders like depression and addiction (Furtado & Katzman, 2015; Hong, Kim, & Im, 2016; Radtke, Chapman, Hall, & Syed, 2017). For example, in animal models, injection of the pro-inflammatory cytokines TNF-α and IL-1β into healthy subjects induces behaviours similar to social withdrawal (Najjar, Pearlman, Alper, Najjar, & Devinsky, 2013). In another example, cytokine dysregulation is

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associated with memory impairment and neuropsychiatric disorders in the developing brain (Bilbo & Schwarz, 2012). A meta-analyses of several studies examining links between inflammation and response to treatment for depression revealed that antidepressants reduce IL-6 levels, regardless of treatment outcome (Strawbridge et al., 2015). Further, they found that elevated TNF-α is associated with treatment resistance, and that treatment non-responders exhibit higher baseline inflammation levels (Strawbridge et al., 2015). Finally, MRI brain scans reveal that inflammatory disease activity is associated with elevated levels of anxiety and depression in multiple sclerosis (MS) patients (Rossi et al., 2017). We have previously speculated that the anti-inflammatory effects of psychedelics mediated through serotonin 5-HT_{2A} receptor activation are a key component of not only the anti-depressant effects of psilocybin, but also contribute to its long-lasting effects after only a single treatment (Kyzar, Nichols, Gainetdinov, Nichols, & Kalueff, 2017). We hypothesize that psychedelics acutely reset resting state functional connectivity (RFSC) to healthy networks to rapidly alleviate depression, then produce long-lasting effects by reducing neuroinflammation and preventing the brain from returning to a persistent inflamed pathological state and accompanying depression. Although serotonin has long been known to be an immune modulator, only relatively recently has activation of 5-HT_{2A} receptors with psychedelics been shown to have potent anti-inflammatory effects. Here, we will discuss serotonin, inflammation, 5-HT_{2A} receptors, and how psychedelics are acting as anti-inflammatory agents.

Serotonin and inflammation

Inflammation is broadly defined as an endogenous repair/host defense mechanism that local and systemic systems mount after a physical, chemical, thermal, or biological insult to remove the offensive agent and promote healing (Medzhitov, 2008; Naik & Wala, 2013). The process not only provides an acute defense against harmful agents and infection, it is heavily involved in the restoration of normal tissue functioning following a traumatic event (Barnes, 2011). The immune response is comprised of innate and adaptive components, which work together to combat noxious stimuli at the point of infection and establish pathogen profiles to vigorously respond to future invasion (Chaplin, 2010). The innate immune response (antigen-independent) responds within minutes to hours of a biological insult, recruiting immune cells to infection sites and promoting inflammation through cytokine release. Cytokines are a large family of small glycosylated proteins that are secreted by innate immune cells, which have pleiotropic and diverse functions in immunoregulation (Barnes, 2009; Naik & Wala, 2013), including mediation of cell-to-cell signalling, chemotaxis, and immunomodulation (Hamid & Tulic, 2009). Key participants such as macrophages of the innate system form the front line of defense, non-discriminately recognizing, ingesting, and destroying pathogens and scavenging debris (Janeway, Walport, & Shlomchik, 2001). Dendritic cells possess phagocytic properties, but also function as antigen-presenting cells (APC) and act as a messenger between the innate and adaptive pathways. The adaptive response is activated when the innate pathways are unable to effectively eliminate the infectious agents. The adaptive immune response's primary function is to recognize 'self' antigens from 'non-self' antigens. Adaptive immune cells like T-helper cells, which are activated through the action of APCs, and lymphocytes recognize foreign invaders and secrete antibodies, which bind to 'non-self' antigens on pathogens and target them for efficient destruction (Warrington, Watson, Kim, & Antonetti, 2011). In the pathological state, the immune system undergoes aberrant and uncontrollable activation, ultimately inducing tissue destruction rather than healing. Diseases such as asthma, allergic rhinitis, and autoimmune diseases like Type 1 diabetes, rheumatoid arthritis (RA), and lupus all stem from an overactive immune system (Shah, 2012). Traditional treatments for an overactive immune system or an exaggerated hypersensitivity reaction aim to prevent or reduce the inflammatory response or suppress the immune system itself (Brower, 2004).

Serotonin is heavily involved in inflammation and the inflammatory response (Shajib & Khan, 2015) and is seen as primarily pro-inflammatory. For example, it plays a key role in the generation of inflammation in the gut (Ghia et al., 2009), and fluctuations in serotonin levels are associated with damage to the liver (Nocito et al., 2007) and pancreas (Sonda et al., 2013). Accordingly, depletion of serotonin reduces inflammation in a number of different animal disease models (Harbuz, Marti, Lightman, & Jessop, 1998; Harbuz et al., 1996; Margolis et al., 2014; Pierce, Xie, Peroutka, Green, & Levine, 1995). In blood samples taken from healthy volunteers, elevated serotonin is associated with higher levels of the proinflammatory cytokines IL-6 and TNF-α, with diminished serotonin levels associated with a lower expression of these markers (Kubera, Maes, Kenis, Kim, & Lason, 2005). In lipopolysaccharide (LPS)-primed monocytes,

serotonin modulates cytokine and chemokine production via activation of 5-HT_3, 5-HT_4, and 5-HT_7 receptors (Dürk et al., 2005). Serotonin can also activate human monocytes and prevent their apoptosis (Soga, Katoh, Inoue, & Kishimoto, 2007).

Serotonin and the 5-HT_{2A} receptor

Serotonin produces its effects through interactions with target receptor proteins. Of the 14 known mammalian serotonin receptors, 13 are G protein-coupled receptors (GPCRs). GPCRs represent the largest family of membrane proteins in the human genome, with over 800 identified sequences (Fredriksson, Lagerstrom, Lundin, & Schioth, 2003). GPCRs are comprised of seven transmembrane-spanning alpha helices joined by hydrophilic extracellular (N terminus) and intracellular (C terminus) loops (Allen & Roth, 2011; Palczewski et al., 2000). Upon agonist binding, GPCRs undergo a conformational change that ultimately triggers a biological response through the activation of intracellular transducers, namely coupled G proteins (G_i/G_o, G_s, G_q) and β–arrestin (Kenakin, 2010; Roth & Kroeze, 2015). Mutations in GPCR gene sequences have been linked to several diseases (McAlear, Kraft, & Gross, 2010; Moore et al., 2016; Samson et al., 1996). Pharmacologically, GPCRs are attractive drug targets. GPCRs possess roles in nearly every biological process, and their location on the cell surface is easily accessible (Mason, Bortolato, Congreve, & Marshall, 2012). Approximately 30% of all FDA-approved medications and ~65% of prescription medications are directed towards GPCRs (Drews, 2000; Wacker, Stevens, & Roth, 2017), which account for ~300 distinct molecular targets (Overington, Al-Lazikani, & Hopkins, 2006).

Serotonin receptors are prevalent throughout the body (McCorvy & Roth, 2015), and regulate a range of diverse processes such as learning and memory (Domeney et al., 1991), control of sleep/wake cycles (Jouvet, Bobillier, Pujol, & Renault, 1967), thermoregulation (Ray et al., 2011), appetite (Fuxe, Farnebo, Hamberger, & Ogren, 1975), sexual behaviour in males and females (Ahlenius, Larsson, & Svensson, 1980; Meyerson & Lewander, 1970), pain (Sparkes & Spencer, 1971), motor activity (Mabry & Campbell, 1973), and aspects of autonomic function like arterial pressure and heart rate (Darmon, Awabdh, Emerit, & Masson, 2015; Laguzzi, Reis, & Talman, 1984). Accordingly, dysfunction in the serotoninergic system is associated with several diseases and disorders, like anxiety and depression (Thiebot, 1986), migraine headaches (Graham, 1964), schizophrenia (Meltzer, 1995), emesis, obsessive-compulsive disorders, drug addiction, and neurodegenerative disorders (Filip & Bader, 2009; Giulietti et al., 2014; Politis & Loane, 2011). Serotenergic dysregulation has also been implicated in diseases in peripheral tissues, such as pulmonary hypertension (Egermayer, Town, & Peacock, 1999), cancer of the bile duct (Alpini et al., 2008), chronic kidney failure (Steyn, Viljoen, Ubbink, van Rensburg, & Reinach, 1992), and inflammatory bowel disease (Khan, 2013).

The serotonin receptor family is the largest family of GPCR neurotransmitter receptors (Nichols & Nichols, 2008) and is comprised of seven different receptor families (5-HT_{1-7}). There are 14 distinct subtypes in mammals characterized by amino acid sequence, gene organization, and second messenger coupling pathways (Hoyer et al., 1994). With the exception of the 5-HT_3 receptor, which is a ligand-gated ion channel (Derkach, Surprenant, & North, 1989), all are GPCRs. In general, the 5-HT_1 and 5-HT_5 families couple with $G_{\alpha i/o}$ to inhibit adenylate cyclase (AC) activity, the 5-HT_4, 5-HT_6, and 5-HT_7 families couple with $G_{\alpha s}$ to promote AC activation, and the 5-HT_2 family couples with $G_{\alpha q/11}$ to stimulate phospholipase C (PLC) (Giulietti et al., 2014; Raymond et al., 2001). The receptor sub-type most closely linked to complex behaviours is the 5-HT_{2A} receptor, which is the most widely expressed mammalian serotonin receptor throughout the brain and body (McBride, Mann, McEwen, & Biegon, 1983; Nagatomo, Rashid, Abul Muntasir, & Komiyama, 2004; Nichols, Johnson, & Nichols, 2017; Roth, Berry, Kroeze, Willins, & Kristiansen, 1998; Sonier, Lavigne, Arseneault, Ouellette, & Vaillancourt, 2005). Much work has been done investigating the role of the $G_{\alpha q}$-coupled 5-HT_{2A} receptors within the brain, as they have been shown to participate in processes like cognition and memory (Williams, Rao, & Goldman-Rakic, 2002), and alterations in 5-HT_{2A} receptor signalling have been implicated in disorders like schizophrenia (Vollenweider, Vollenweider-Scherpenhuyzen, Babler, Vogel, & Hell, 1998; Williams et al., 2002). Within the vasculature, 5-HT_{2A} receptors are believed to modulate aspects of vasoconstriction and cardiomyocyte proliferation (Brattelid et al., 2007; Cogolludo et al., 2006; McKune & Watts, 2001; Nichols, 2009). The role of the 5-HT_{2A} receptor in other tissue like renal cells, lymphocytes, fibroblasts, and hepatic cells is far less defined, but it has been linked to cellular proliferation and differentiation (Göőz, Göőz, Luttrell, & Raymond, 2006; Pellegrino & Bayer, 2002; Ruddell et al., 2006; Welsh, Harnett, MacLean, & Peacock, 2004).

5-HT$_{2A}$ receptors and the immune system

The 5-HT$_{2A}$ receptor has a wide distribution in peripheral tissues. Significantly, the 5-HT$_{2A}$ receptor mRNA has been detected in many immune related tissues like the spleen, thymus, and circulating lymphocytes (Stefulj, Jernej, Cicin-Sain, Rinner, & Schauenstein, 2000). 5-HT$_{2A}$ receptor protein is expressed in components of both the innate and adaptive immune response, including human peripheral blood mononuclear cells (PBMCs) (Cloez-Tayarani, Petit-Bertron, Venters, & Cavaillon, 2003), eosinophils (Kang et al., 2013), and T cells (Aune, Kelley, Ranges, & Bombara, 1990; Herr, Bode, & Duerschmied, 2017; Inoue et al., 2011). Early attempts to identify the role of the 5-HT$_{2A}$ receptor in the immune response produced contradictory results. Arzt, Costas, Finkielman, and Nahmod (1991) first showed that serotonin could inhibit the synthesis of TNF-α in human monocytes, an effect that was blocked by the 5-HT$_2$ receptor antagonist ketanserin. Later, Ito, Ikeda, Shimpo, Yamamoto, and Shimada (2000) found that agonism of 5-HT$_2$ receptors in human vascular smooth muscle cells elevated production of the inflammatory cytokine IL-6, whereas antagonism resulted in diminished IL-6 production. Other groups found that one of the antagonists from Ito et al.'s study, sarpogrelate, reduced the expression of a number of pro-inflammatory mediators (Akiyoshi et al., 2006; Marconi, Darquenne, Boulmerka, Mosnier, & D'Alessio, 2003). Blockade of the 5-HT$_2$ receptor using ketanserin has also been shown to modestly down-regulate inflammation and eosinophil infiltration in a mouse model of allergic asthma (De Bie et al., 1998). Unfortunately, ketanserin has high affinity for blockade of the histamine H1 receptor, which may have contributed to its perceived anti-inflammatory effects in these assays. An early experiment directly activating 5-HT$_2$ receptors with (*R*)-DOI found that the drug partially blocked LPS and TNF-α stimulated nitrite accumulation in rat C6 glioma cells (Miller & Gonzalez, 1998; Miller, Mariano, & Cruz, 1997). Despite these contradictory findings, with most studies supporting the role of 5-HT$_2$ receptor activation as proinflammatory, these studies supported the notion that 5-HT$_{2A}$ receptors are involved in the immune response. In CBA mice (*R*)-DOI suppresses the immune response and reduces spleen and peripheral blood CD8(+) T cells counts with cytotoxic/suppressor function (Davydova, Cheido, Gevorgyan, & Idova, 2010). Ketanserin blocks this effect and causes an increase in CD8(+) T cell counts in the spleen, which may indicate that 5-HT$_2$ receptors function in immunosuppressive capacities.

Anti-inflammatory effects of 5-HT$_{2A}$ receptor activation with psychedelics

While studying the effects of the psychedelic drug and selective 5-HT$_2$ receptor agonist (*R*)-2,4-dimethoxy-4-iodoamphetamine [(*R*)-DOI] on the response to TNF-α on rat aortic smooth muscle cells, Yu et al. (2008) discovered that activation of 5-HT$_{2A}$ receptors with psychedelics produces a potent anti-inflammatory effect. Although multiple 5-HT$_{2A}$ agonists tested were shown to have potent anti-inflammatory effects (including lysergic acid diethylamide), (*R*)-DOI was super potent to repress TNF-α induced inflammation at levels in the low picomolar range (IC$_{50}$ concentrations 10–20 pM). (*R*)-DOI inhibited the TNF-α induced expression of genes encoding *intracellular adhesion molecule-1* (ICAM-1), *vascular cell adhesion molecule-1* (VCAM-1), and inflammatory cytokine *IL-6*. (*R*)-DOI also blocked activation and nuclear translocation of NF-κB, and nitric oxide synthase activity. 5-HT$_{2B}$ and 5-HT$_{2C}$ receptor selective agonists were unable to repress TNF-α mediated inflammation, demonstrating that the anti-inflammatory effects were specific for 5-HT$_{2A}$ receptor activation. Complete blockades of the effects of TNF-α were observed when (*R*)-DOI was added to cells simultaneously with TNF-α, and (*R*)-DOI was also effective in significantly attenuating TNF-α induced inflammation when added several hours after TNF-α stimulation. These data suggested 5-HT$_{2A}$ receptor activation may be a viable therapeutic strategy for persistent and chronic inflammation, and not just a preventative treatment (Pelletier & Siegel, 2009).

Although all psychedelics tested were anti-inflammatory, the super-potency of (*R*)-DOI was unexpected, because other structurally similar psychedelics were orders of magnitude less potent. From a structural standpoint, (*R*)-DOI is a phenethylamine (Nichols, 2012) and related to mescaline. Mescaline naturally occurs in the peyote cactus (*Lophophora williamsii*), and was first isolated by the chemist Dr Arthur Heffter in 1898 (Heffter, 1898). Not only has peyote been consumed by Native North Americans for millennia for religious ceremonies (Bruhn, De Smet, El-Seedi, & Beck, 2002), it has also been shown to activate several immune parameters (nitric oxide and cytokine production in macrophages and lymphocyte proliferation) and directly kill tumour cells (Franco-Molina et al., 2003). In the mid 20th century, the mescaline structural template was used to develop a series of hallucinogenic phenethylamines (Hey, 1947; Peretz, Smythies, & Gibson, 1955; Shulgin, Sargent, & Naranjo, 1969). One of these, (*R*)-DOI,

was found to selectively label 5-HT_2 receptors in studies incorporating a radioactive iodine isotope (Johnson, Hoffman, Nichols, & Mathis, 1987; McKenna et al., 1989), and currently represents one of the best tools for pharmacologists to study selective activation of 5-HT_2 receptors. Subjectively, the behavioural effects of (*R*)-DOI in humans are similar to those of LSD; however, the duration is significantly longer (> 24 h vs ~8 h), and there are reported differences in tactile body sensation (i.e. muscle tension, nausea, etc.) (Shulgin, 1991).

Moving from *in vitro* to *in vivo*, Nau, Yu, Martin, and Nichols (2013) investigated the effects of (*R*)-DOI to block the effects of TNF-α in a live animal. For these *in vivo* experiments, mice were intraperitoneally injected with saline, TNF-α, or (*R*)-DOI 30 min prior to TNF-α. The highest dose of (*R*)-DOI administered, 0.3 μg/kg, represents the behavioural threshold of (*R*)-DOI in C57BL/6J mice (the lowest dose necessary to elicit a behavioural response) (Smith, Barrett, & Sanders-Bush, 2003). After 5 h of treatment, tissues and blood were removed for analysis by gene expression and protein assays. Anti-inflammatory effects were found in several tissues, including the aortic arch, intestine, and blood of the (*R*)-DOI treated animals. In these tissues, (*R*)-DOI blocked TNF-α induced expression of ICAM-1, VCAM-1, cytokines IL-6 and IL-1b, chemokines monocyte chemotactic protein-1 (MCP-1), C-X3-C motif ligand 1 (Cx3Cll), and increases in circulating IL-6. The 5-HT_{2A} receptor selective antagonist M100109 was used as a control to demonstrate that the anti-inflammatory effects were indeed mediated by selective activation of 5-HT_{2A} receptors.

If serotonin acting at the 5-HT_{2A} receptor is primarily pro-inflammatory, as described in the historical literature, why are psychedelics anti-inflammatory at the same receptor? We hypothesize that the anti-inflammatory effects of (*R*)-DOI and other psychedelics may be partially explained by functional selectivity. Functional selectivity is a concept where different drugs induce different conformations of the same receptor to recruit and activate different effector pathways (Kenakin, 2011; Urban et al., 2007). In this scenario, serotonin primarily stabilizes the receptor in a conformation that recruits pro-inflammatory pathways, whereas psychedelics stabilize the receptor in a slightly different conformation that recruits anti-inflammatory signalling pathways. This would also explain why certain antagonists at the receptor also have been shown to have anti-inflammatory properties, because they would be preventing the effects of serotonin itself to promote inflammation. Although the precise molecular mechanisms remain to be elucidated, we hypothesize that 5-HT_{2A} receptor activation with psychedelics leads to a functionally selective recruitment of anti-inflammatory effector pathways that lead to disruption of either activation of or downstream signalling from TNF-α receptors and targets like NF-κB.

5-HT_{2A} receptors and asthma

Asthma is an inflammatory disorder characterized by varying degrees of airflow obstruction, airway hyperresponsiveness (AHR), mucus over-production, and bronchial inflammation (Busse & Lemanske, 2001). The inflammation developed in asthmatic lungs stems from an aberrant expansion of inflammatory cells such as eosinophils, mast cells, and activated T-helper lymphocytes (Hamid & Tulic, 2009). These cells produce pro-inflammatory factors such as cytokines, chemokines, growth factors, lipid mediators, immunoglobins, and histamine, which ultimately contribute to remodelling of the airways (Barnes, 2011; Deckers, Branco Madeira, & Hammad, 2013). 5-HT_{2A} mRNA is expressed at elevated levels in numerous immune related cell types that contribute to the pathophysiology of inflammation (Stefulj et al., 2000) and asthma that include CD4+ T-cells, alveolar macrophages, eosinophils, and lung epithelial and bronchial smooth muscle cells (Kang et al., 2013; Leon-Ponte, Ahern, & O'Connell, 2007; Mikulski et al., 2010). An example of the role of 5-HT_{2A} receptors in these processes is that migration of eosinophils to the lung depends on 5-HT_{2A} receptor activation in eosinophils. Therefore, asthma was an attractive disorder to test the efficacy of (*R*)-DOI, for which there was a robust animal model.

Multiple models of murine allergic airways disease exist, with most involving the repeated exposure of the animal to some allergen (usually either chicken egg albumin [OVA] or house dust mite antigen) followed by an analysis of airway structural remodelling and lung function, inflammatory cell infiltration, mucus production, and inflammatory mediator expression (Locke, Royce, Wainewright, Samuel, & Tang, 2007). OVA treatment in mice (sensitization with systemic OVA to induce an IgE response, and then exposure to inhaled OVA to induce an allergic reaction in the lung, Figure 1) recapitulates several hallmark symptoms of human allergic asthma including pulmonary inflammation, AHR, mucus over-production, and eosinophilia. Consistent with the previously observed potencies of (*R*)-DOI to prevent

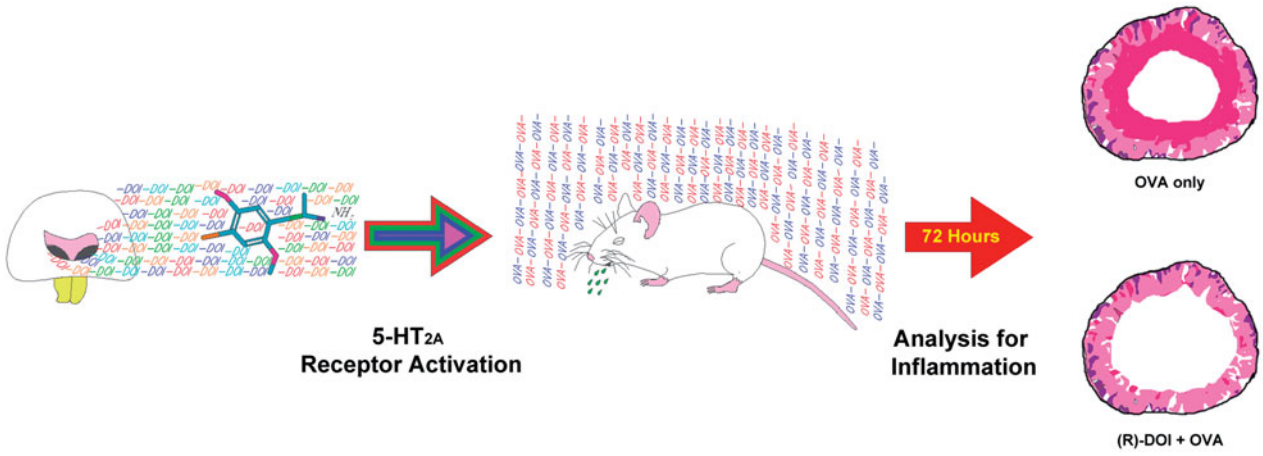

Figure 1. (*R*)-DOI administration in a mouse acute asthma model. Mice are first intranasally exposed to nebulized (*R*)-DOI. (*R*)-DOI at dosages that are orders of magnitude below those necessary to elicit a behavioural response produce full therapeutic efficacy. Following a period of 30 min, which allows for full 5-HT_{2A} receptor activation, the animals are exposed to aerosolized ovalbumin. Histological analysis reveals that animals treated with (*R*)-DOI prior to OVA exposure exhibit normal airways morphology, whereas untreated animals exposed to OVA have thickened airways with peribronchial inflammation and a significant degree of mucus-cell infiltration (pink staining). The strength of (*R*)-DOI as an anti-inflammatory agent can be further illustrated via techniques using forced ventillation and whole-body plethysmography (WBP) to monitor pulmonary mechanics, flow cytometry for cellular analysis, and qRT-PCR for cytokine and chemokine expression.

inflammation, nasally-administered (*R*)-DOI at doses as low as 0.01 mg/kg completely prevents AHR, eosinophilia, and pulmonary inflammation (Nau et al., 2015). Significantly, this dose is far below what is necessary to elicit a behavioural response. We have found that several other psychedelic compounds also prevent the development of asthma, indicating that this property is not unique to (*R*)-DOI (unpublished data). Gene expression analysis revealed that only some pro-inflammatory cytokines were suppressed by (*R*)-DOI treatment and included *gm-csf*, *Il5*, and *Il13* (Nau et al., 2015). Other cytokines previously implicated in the pathophysiology of asthma, like *Il4*, were not. Flow cytometry of dissociated lung cells showed that (*R*)-DOI also reduced Th2 cell recruitment and polarization in the treated animals compared to sham treated asthmatic mice (Nau et al., 2015).

Current asthma therapies include *β*2-adrenergic receptor agonists, which simply induce smooth muscle relaxation and bronchodilation, and glucocorticoids, which bluntly repress the entire immune system and are ineffective in a significant sub-set of patients (Booth et al., 1995; Chung & Wenzel, 2014; Godfrey et al., 1995; Hekking et al., 2015; Jeffery et al., 1992). Although newer biologics like benralizumab are coming to the market, which are antibodies specific to either a cytokine or its receptor, they are very expensive, require infusion in the clinic, and are only approved for more treatment resistant severe forms of asthma (Darveaux & Busse, 2015; Quirce, Phillips-Angles, Dominguez-Ortega, & Barranco, 2017). Therefore, (*R*)-DOI and/or other psychedelics potentially represent a new class of disease-modifying, steroid sparing, small molecule therapeutics for the treatment of asthma.

Conclusion

Psychedelics produce a potent blockade of the inflammation produced by TNF-α in cell and animal models of inflammation. Because of TNF-α's controversial role in asthma (Nakae et al., 2007) and (*R*)-DOI's impact on numerous factors contributing to the differentiation of multiple immune cells (Kim, DeKruyff, & Umetsu, 2010; Moreira & Hogaboam, 2011), we believe that the effects of 5-HT_{2A} receptor activation likely extend far beyond the mere blockade of TNF-α signalling. Given the select nature by which (*R*)-DOI only blocks sub-sets of pro-inflammatory mediator expression, psychedelics may modulate histone modifications and epigenetic signalling for their therapeutic effects. In asthma, an interplay between the acetylation and deacetylation states of histones in inflammatory genes has been well documented (Adcock, Tsaprouni, Bhavsar, & Ito, 2007; Cosio et al., 2004; Gunawardhana, Gibson, Simpson, Powell, & Baines, 2014; K. Ito et al., 2002). Furthermore, histone deacetylase (HDAC) inhibitors have been shown to reduce eosinophilic inflammation and AHR in mouse models of asthma (Choi et al., 2005; Ren et al., 2016). It is

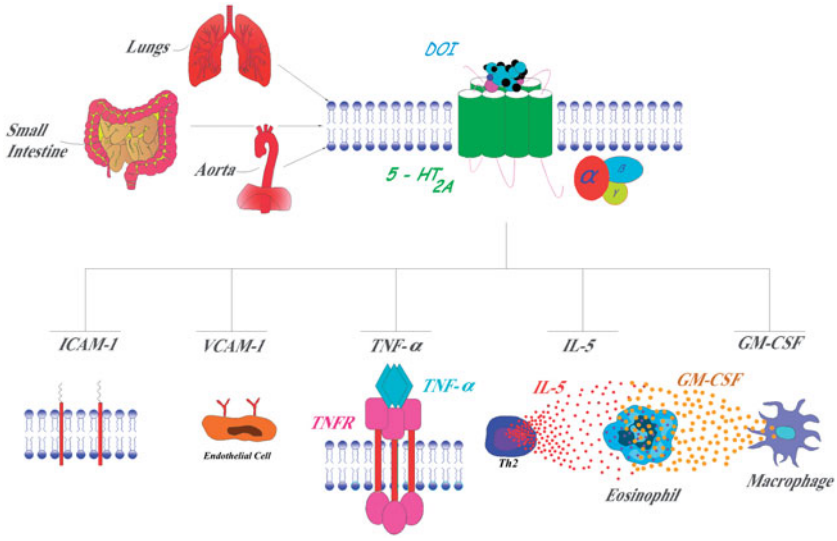

Figure 2. 5-HT_{2A} receptor activation represses the expression of inflammatory mediators in multiple tissues. Mice treated with (*R*)-DOI have been shown to have suppressed cytokine and chemokine expression following TNF-α-stimulation (aortic arch, small intestine) and ovalbumin challenge (lung). Intracellular adhesion molecule-1 (ICAM-1) is found on the surface of endothelial and smooth muscle cells and contributes to the inflammatory response by promoting the adhesion of immune cells onto the endothelial surface, allowing for their subsequent infiltration into peripheral tissues. Vascular cell adhesion molecule-1 is also found on the surface of endothelial cells and serves as a scaffold for leukocyte migration via reactive oxygen species (ROS) and antioxidants. TNF-α is a key mediator in the inflammatory response and activates numerous pro-inflammatory signal transduction pathways. IL-5 is a Th2-derived cytokine that promotes prolonged eosinophil survival. Granulocye-macrophage colony-stimulating factor (GM-CSF) is secreted by macrophages and recruits immune cells (i.e. eosinophils) to inflammation sites and induces their differentiation to pro-inflammatory phenotypes. Together the action of 5-HT_{2A} agonists on these inflammatory markers indicate therapeutic value for a number of disorders, including asthma, atherosclerosis, irritable bowel syndrome, rheumatoid arthritis, diabetes, and even depression.

certainly plausible that 5-HT_{2A} receptor activation modulates histone acetylation and methylation patterns to promote the expression of anti-inflammatory genes and repress the expression of pro-inflammatory genes. Only recently has it been established that 5-HT_{2A} receptor activity can alter epigenetic factors (Holloway & Gonzalez-Maeso, 2015).

The remaining questions regarding psychedelics and inflammation include: do 5-HT_{2A} agonists have more pronounced effects in some cell types more than others (i.e. do the anti-inflammatory effects manifest themselves more strongly in macrophages than eosinophils or Th2 cells)? Does 5-HT_{2A} receptor activation modulate differentiation of immune-related cells to more anti-inflammatory phenotypes? What are the effects of chronic administration of a 5-HT_{2A} agonist in peripheral tissues to treat immune-related disorders? Aside from these purely mechanistic questions, it is tempting to speculate on the nature of 5-HT_{2A} receptor activation in other inflammatory disorders. Because 5-HT_{2A} receptor activation impacts the expression of several key inflammatory mediators (Figure 2) and the variety of effects we have observed in animal models of inflammation, we believe that psychedelics may be of therapeutic value to a wide range of inflammatory disorders in humans. With regard to therapeutic aspects of psychiatric disorders like depression, putative suppression of neuroinflammation by psychedelics may play a key role in the long-term stability of the reported anti-depressant effects after a single treatment. Another putative component may be stimulation of neurogenesis. For example, the psychotropic ingredient of the Amazonian tea ayahuasca (Morales-García et al., 2017) can stimulate hippocampal neurogenesis, which has been shown to reduce depression-like behaviours (Hill, Sahay, & Hen, 2015). Although the use of sub-behavioural levels of psychedelics remains to be validated as an effective therapeutic strategy for inflammation in humans, the data from cellular and animal models is promising, and these agents represent small molecule, highly bioavailable, inexpensive, and steroid sparing treatments for inflammatory-related diseases like asthma, atherosclerosis, inflammatory bowel disease, and rheumatoid arthritis. One possible barrier to the development of psychedelics for use in the clinic is that the majority are scheduled and controlled substances in the United States and

several other countries. Nevertheless, drugs that activate the 5-HT_{2A} receptor and that have been shown to produce psychedelic effects in humans have been FDA approved (e.g. lorcaserin). Although the results we discuss here are promising, more research is needed to fully unlock therapeutic potentials and to discover molecular mechanisms underlying their effects.

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