

## REVIEW ARTICLE

# Psychedelics as anti-inflammatory agents

Thomas W. Flanagan and Charles D. Nichols

Department of Pharmacology and Experimental Therapeutics, Louisiana State University Health Sciences Center, New Orleans, LA, USA

### ABSTRACT

Serotonin (5-hydroxytryptamine, 5-HT)<sub>2A</sub> 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<sub>2A</sub> 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<sub>2A</sub> receptor in the inflammatory response, as well as highlight studies using the 5-HT<sub>2A</sub> 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<sub>2A</sub> 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.

### ARTICLE HISTORY

Received 29 January 2018  
Accepted 24 May 2018

### KEYWORDS

Psychedelics; inflammation;  
(*R*)-DOI; 5-HT<sub>2A</sub> receptor;  
5-HT<sub>2A</sub> agonist;  
hallucinogens; DOI

## 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<sub>2A</sub> 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<sub>2A</sub> 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- $\alpha$  and IL-1 $\beta$  into healthy subjects induces behaviours similar to social withdrawal (Najjar, Pearlman, Alper, Najjar, & Devinsky, 2013). In another example, cytokine dysregulation is

associated with memory impairment and neuropsychiatric disorders in the developing brain (Bilbo & Schwarz, 2012). A meta-analysis 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- $\alpha$  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<sub>2A</sub> 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<sub>2A</sub> receptors with psychedelics been shown to have potent anti-inflammatory effects. Here, we will discuss serotonin, inflammation, 5-HT<sub>2A</sub> 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 signaling, 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- $\alpha$ , 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<sub>3</sub>, 5-HT<sub>4</sub>, and 5-HT<sub>7</sub> 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<sub>2A</sub> 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, & Schiöth, 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<sub>i</sub>/G<sub>o</sub>, G<sub>s</sub>, G<sub>q</sub>) and  $\beta$ -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 serotonergic 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<sub>1-7</sub>). 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<sub>3</sub> receptor, which is a ligand-gated ion channel (Derkach, Surprenant, & North, 1989), all are GPCRs. In general, the 5-HT<sub>1</sub> and 5-HT<sub>5</sub> families couple with G<sub>xi/o</sub> to inhibit adenylate cyclase (AC) activity, the 5-HT<sub>4</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub> families couple with G<sub>ss</sub> to promote AC activation, and the 5-HT<sub>2</sub> family couples with G<sub>αq/11</sub> 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<sub>2A</sub> 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<sub>αq</sub>-coupled 5-HT<sub>2A</sub> 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<sub>2A</sub> 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<sub>2A</sub> 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<sub>2A</sub> 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 (Gööz, Gööz, Luttrell, & Raymond, 2006; Pellegrino & Bayer, 2002; Ruddell et al., 2006; Welsh, Harnett, MacLean, & Peacock, 2004).

## 5-HT<sub>2A</sub> receptors and the immune system

The 5-HT<sub>2A</sub> receptor has a wide distribution in peripheral tissues. Significantly, the 5-HT<sub>2A</sub> 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<sub>2A</sub> 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<sub>2A</sub> receptor in the immune response produced contradictory results. Arzt, Costas, Finkielman, and Nahmod (1991) first showed that serotonin could inhibit the synthesis of TNF- $\alpha$  in human monocytes, an effect that was blocked by the 5-HT<sub>2</sub> receptor antagonist ketanserin. Later, Ito, Ikeda, Shimpo, Yamamoto, and Shimada (2000) found that agonism of 5-HT<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> receptors with (R)-DOI found that the drug partially blocked LPS and TNF- $\alpha$  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<sub>2</sub> receptor activation as proinflammatory, these studies supported the notion that 5-HT<sub>2A</sub> 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<sub>2</sub> receptors function in immunosuppressive capacities.

## Anti-inflammatory effects of 5-HT<sub>2A</sub> receptor activation with psychedelics

While studying the effects of the psychedelic drug and selective 5-HT<sub>2</sub> receptor agonist (R)-2,4-dimethoxy-4-iodoamphetamine [(R)-DOI] on the response to TNF- $\alpha$  on rat aortic smooth muscle cells, Yu et al. (2008) discovered that activation of 5-HT<sub>2A</sub> receptors with psychedelics produces a potent anti-inflammatory effect. Although multiple 5-HT<sub>2A</sub> agonists tested were shown to have potent anti-inflammatory effects (including lysergic acid diethylamide), (R)-DOI was super potent to repress TNF- $\alpha$  induced inflammation at levels in the low picomolar range (IC<sub>50</sub> concentrations 10–20 pM). (R)-DOI inhibited the TNF- $\alpha$  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- $\kappa$ B, and nitric oxide synthase activity. 5-HT<sub>2B</sub> and 5-HT<sub>2C</sub> receptor selective agonists were unable to repress TNF- $\alpha$  mediated inflammation, demonstrating that the anti-inflammatory effects were specific for 5-HT<sub>2A</sub> receptor activation. Complete blockades of the effects of TNF- $\alpha$  were observed when (R)-DOI was added to cells simultaneously with TNF- $\alpha$ , and (R)-DOI was also effective in significantly attenuating TNF- $\alpha$  induced inflammation when added several hours after TNF- $\alpha$  stimulation. These data suggested 5-HT<sub>2A</sub> 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<sub>2</sub> 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<sub>2</sub> 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- $\alpha$  in a live animal. For these *in vivo* experiments, mice were intraperitoneally injected with saline, TNF- $\alpha$ , or (R)-DOI 30 min prior to TNF- $\alpha$ . The highest dose of (R)-DOI administered, 0.3  $\mu$ g/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- $\alpha$  induced expression of ICAM-1, VCAM-1, cytokines IL-6 and IL-1b, chemokines monocyte chemoattractant protein-1 (MCP-1), C-X3-C motif ligand 1 (Cx3CL1), and increases in circulating IL-6. The 5-HT<sub>2A</sub> 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<sub>2A</sub> receptors.

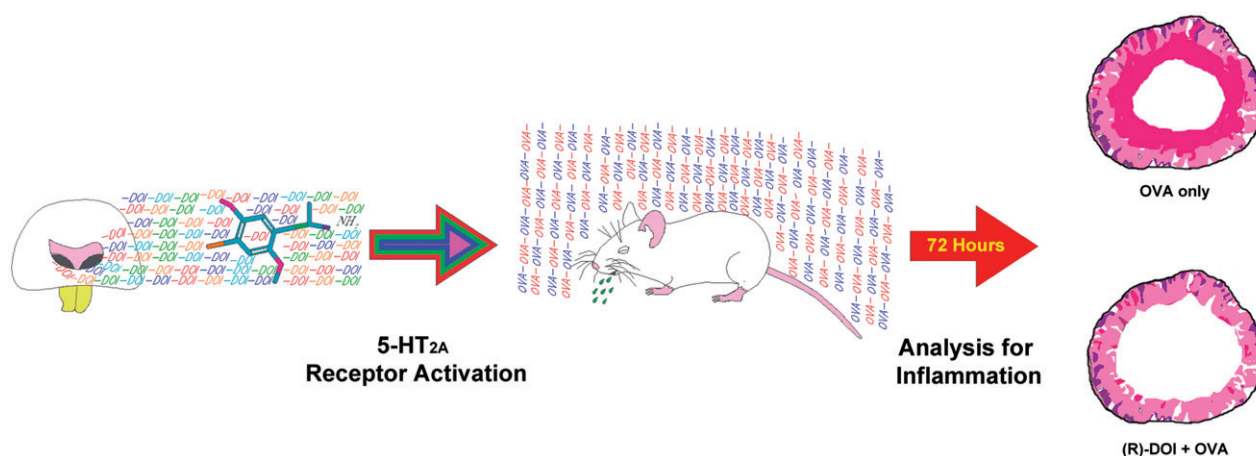
If serotonin acting at the 5-HT<sub>2A</sub> receptor is primarily pro-inflammatory, as described in the historical literature, why are psychedelics anti-inflammatory at the same receptor? We hypothesize that the anti-inflammatory effects of (R)-DOI and other psychedelics may be partially explained by 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<sub>2A</sub> 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- $\alpha$  receptors and targets like NF- $\kappa$ B.

### 5-HT<sub>2A</sub> receptors and asthma

Asthma is an inflammatory disorder characterized by varying degrees of airflow obstruction, airway hyper-responsiveness (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<sub>2A</sub> 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<sup>+</sup> 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<sub>2A</sub> receptors in these processes is that migration of eosinophils to the lung depends on 5-HT<sub>2A</sub> 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, Wainwright, 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<sub>2A</sub> 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 ventilation and whole-body plethysmography (WBP) to monitor pulmonary mechanics, flow cytometry for cellular analysis, and qRT-PCR for cytokine and chemokine expression.

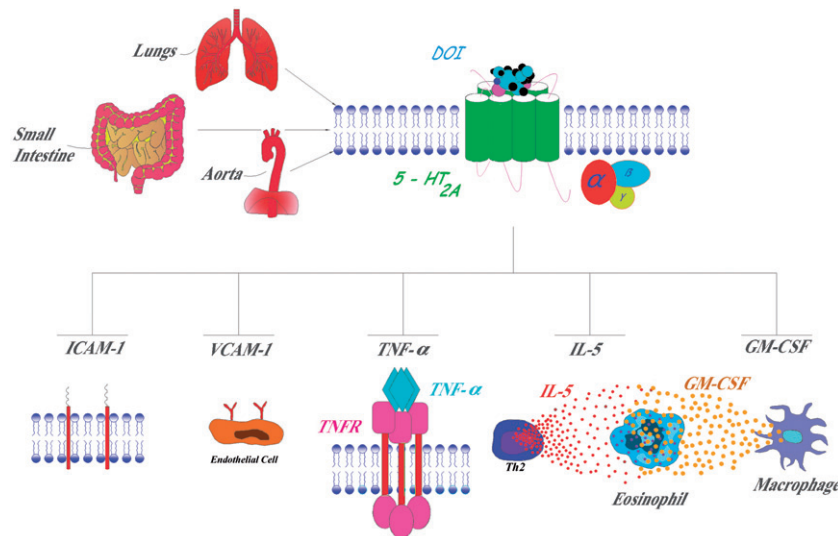
inflammation, nasally-administered (R)-DOI at doses as low as 0.01 mg/kg completely prevents AHR, eosinophilia, and pulmonary inflammation (Nau et al., 2015). Significantly, this dose is far below what is necessary to elicit a behavioural response. We have found that several other psychedelic compounds 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  $\beta_2$ -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- $\alpha$  in cell and animal models of inflammation. Because of TNF- $\alpha$ '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<sub>2A</sub> receptor activation likely extend far beyond the mere blockade of TNF- $\alpha$  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<sub>2A</sub> 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- $\alpha$ -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- $\alpha$  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. Granulocyte-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<sub>2A</sub> 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<sub>2A</sub> 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<sub>2A</sub> receptor activity can alter epigenetic factors (Holloway & Gonzalez-Maeso, 2015).

The remaining questions regarding psychedelics and inflammation include: do 5-HT<sub>2A</sub> 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<sub>2A</sub> receptor activation modulate differentiation of immune-related cells to more anti-inflammatory phenotypes? What are the effects of chronic administration of a 5-HT<sub>2A</sub> 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<sub>2A</sub> receptor activation in other inflammatory disorders. Because 5-HT<sub>2A</sub> 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<sub>2A</sub> 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.

## Acknowledgement

Special thanks to Blake A. DeVellis for the drafting and assembly of figures.

## Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

## Funding

Support for our work comes from a sponsored research contract from the Eleusis Benefit Corporation, and a Scholar Award from the American Asthma Foundation awarded to Charles D. Nichols.

## References

- Adcock, I. M., Tsaprouni, L., Bhavsar, P., & Ito, K. (2007). Epigenetic regulation of airway inflammation. *Current Opinion in Immunology*, 19, 694–700. doi:10.1016/j.coi.2007.07.016
- Ahlenius, S., Larsson, K., & Svensson, L. (1980). Further evidence for an inhibitory role of central 5-HT in male rat sexual behavior. *Psychopharmacology (Berl)*, 68, 217–220. doi:10.1007/BF00428106
- Akiyoshi, T., Zhang, Q., Inoue, F., Aramaki, O., Hatano, M., Shimazu, M., ... Niimi, M. (2006). Induction of indefinite survival of fully mismatched cardiac allografts and generation of regulatory cells by sarpogrelate hydrochloride. *Transplantation*, 82, 1051–1059. doi:10.1097/01.tp.0000233870.54297.9a
- Allen, J. A., & Roth, B.L. (2011). Strategies to discover unexpected targets for drugs active at G protein-coupled receptors. *Annual Review of Pharmacology and Toxicology*, 51, 117–144. doi:10.1146/annurev-pharmtox-010510-100553
- Alpini, G., Invernizzi, P., Gaudio, E., Venter, J., Kopriva, S., Bernuzzi, F., ... DeMorrow, S. (2008). Serotonin metabolism is dysregulated in cholangiocarcinoma, which has implications for tumor growth. *Cancer Research*, 68, 9184–9193. doi:10.1158/0008-5472.CAN-08-2133
- Arzt, E., Costas, M., Finkielman, S., & Nahmod, V., E. (1991). Serotonin inhibition of tumor necrosis factor- $\alpha$  synthesis by human monocytes. *Life Sciences*, 48, 2557–2562. doi:10.1016/0024-3205(91)90612-F
- Aune, T., M., Kelley, K., A., Ranges, G., E., & Bombara, M., P. (1990). Serotonin-activated signal transduction via serotonin receptors on Jurkat cells. *The Journal of Immunology*, 145, 1826–1831.
- Barnes, P., J. (2009). *Asthma and COPD: basic mechanisms and clinical management*. Amsterdam; Boston: Elsevier/Academic Press.
- Barnes, P.J. (2011). Pathophysiology of allergic inflammation. *Immunological Reviews*, 242, 31–50. doi:10.1111/j.1600-065X.2011.01020.x
- Bilbo, S. D., & Schwarz, J.M. (2012). The immune system and developmental programming of brain and behavior. *Frontiers in Neuroendocrinology*, 33, 267–286. doi:10.1016/j.yfrne.2012.08.006
- Booth, H., Richmond, I., Ward, C., Gardiner, P. V., Harkawat, R., & Walters, E.H. (1995). Effect of high dose inhaled fluticasone propionate on airway inflammation in asthma. *American Journal of Respiratory and Critical Care Medicine*, 152, 45–52. doi:10.1164/ajrccm.152.1.7599861
- Brattellid, T., Qvigstad, E., Birkeland, J.A.K., Swift, F., Bekkevold, S.V.S., Krobert, K. A., ... Sjaastad, I. (2007). Serotonin responsiveness through 5-HT<sub>2A</sub> and 5-HT<sub>4</sub> receptors is differentially regulated in hypertrophic and failing rat cardiac ventricle. *Journal of Molecular and Cellular Cardiology*, 43, 767–779. doi:10.1016/j.yjmcc.2007.08.019
- Brower, V. (2004). When the immune system goes on the attack. *EMBO Reports*, 5, 757–760. doi:10.1038/sj.embor.7400217
- Bruhn, J. G., De Smet, P. A., El-Seedi, H. R., & Beck, O. (2002). Mescaline use for 5700 years. *Lancet*, 359, 1866. doi:10.1016/s0140-6736(02)08701-9
- Busse, W. W., & Lemanske, R. F. Jr. (2001). Asthma. *The New England Journal of Medicine*, 344, 350–362. doi:10.1056/nejm200102013440507
- Carhart-Harris, R. L., Bolstridge, M., Day, C., M., J., Rucker, J., Watts, R., Erritzoe, D., E., ... Nutt, D., J. (2017a). Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. *Psychopharmacology (Berl)*, 235, 399–408. doi:10.1007/s00213-017-4771-x
- Carhart-Harris, R. L., Bolstridge, M., Rucker, J., Day, C.M.J., Erritzoe, D., Kaelen, M., ... Nutt, D.J. (2016a). Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *Lancet Psychiatry*, 3, 619–627. doi:10.1016/s2215-0366(16)30065-7
- Carhart-Harris, R. L., Erritzoe, D., Williams, T., Stone, J. M., Reed, L. J., Colasanti, A., ... Nutt, D.J. (2012). Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proceedings of the National Academy of Sciences of the United States of America*, 109, 2138–2143. doi:10.1073/pnas.1119598109
- Carhart-Harris, R. L., Muthukumaraswamy, S., Roseman, L., Kaelen, M., Droog, W., Murphy, K., ... Nutt, D.J. (2016b). Neural correlates of the LSD experience revealed by multimodal neuroimaging. *Proceedings of the National Academy of Sciences of the United States of America*, 113, 4853–4858. doi:10.1073/pnas.1518377113
- Carhart-Harris, R. L., Roseman, L., Bolstridge, M., Demetriou, L., Pannekoek, J. N., Wall, M. B., ... Nutt, D.J. (2017b). Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. *Scientific Reports*, 7, 13187. doi:10.1038/s41598-017-13282-7

- Chaplin, D.D. (2010). Overview of the immune response. *Journal of Allergy and Clinical Immunology*, 125, S3–S23. doi:10.1016/j.jaci.2009.12.980
- Choi, J. H., Oh, S. W., Kang, M. S., Kwon, H. J., Oh, G. T., & Kim, D.Y. (2005). Trichostatin A attenuates airway inflammation in mouse asthma model. *Clinical & Experimental Allergy*, 35, 89–96. doi:10.1111/j.1365-2222.2004.02006.x
- Chung, K. F., & Wenzel, S. (2014). From the authors: International European Respiratory Society/American Thoracic Society guidelines on severe asthma. *European Respiratory Journal*, 44, 1378–1379. doi:10.1183/09031936.00120714
- Cloez-Tayarani, I., Petit-Bertron, A. F., Venters, H. D., & Cavaillon, J.M. (2003). Differential effect of serotonin on cytokine production in lipopolysaccharide-stimulated human peripheral blood mononuclear cells: involvement of 5-hydroxytryptamine<sub>2A</sub> receptors. *International Immunology*, 15, 233–240.
- Cogolludo, A., Moreno, L., Lodi, F., Frazziano, G., Cobeno, L., Tamargo, J., & Perez-Vizcaino, F. (2006). Serotonin inhibits voltage-gated K<sup>+</sup> currents in pulmonary artery smooth muscle cells: role of 5-HT<sub>2A</sub> receptors, caveolin-1, and KV1.5 channel internalization. *Circulation Research*, 98, 931–938. doi:10.1161/01.RES.0000216858.04599.e1
- Cosio, B. G., Mann, B., Ito, K., Jazrawi, E., Barnes, P. J., Chung, K. F., & Adcock, I.M. (2004). Histone acetylase and deacetylase activity in alveolar macrophages and blood monocytes in asthma. *American Journal of Respiratory and Critical Care Medicine*, 170, 141–147. doi:10.1164/rccm.200305-659OC
- Darmon, M. A., Awabdh, S., Emerit, M. B., & Masson, J. (2015). Insights into Serotonin Receptor Trafficking: Cell Membrane Targeting and Internalization. *Progress in Molecular Biology and Translational Science*, 132, 97–126. doi:10.1016/bs.pmbts.2015.02.009
- Darveaux, J., & Busse, W.W. (2015). Biologics in asthma—the next step toward personalized treatment. *The Journal of Allergy and Clinical Immunology: In Practice*, 3, 152–160. quiz 161. doi:10.1016/j.jaip.2014.09.014
- Davydova, S. M., Cheido, M. A., Gevorgyan, M. M., & Idova, G.V. (2010). Effects of 5-HT<sub>2A</sub> receptor stimulation and blocking on immune response. *Bulletin of Experimental Biology and Medicine*, 150, 219–221.
- De Bie, J. J., Henricks, P. A., Cruikshank, W. W., Hofman, G., Jonker, E. H., Nijkamp, F. P., & Van Oosterhout, A.J. (1998). Modulation of airway hyperresponsiveness and eosinophilia by selective histamine and 5-HT receptor antagonists in a mouse model of allergic asthma. *British Journal of Pharmacology*, 124, 857–864. doi:10.1038/sj.bjp.0701901
- Deckers, J., Branco Madeira, F., & Hammad, H. (2013). Innate immune cells in asthma. *Trends in Immunology*, 34, 540–547. doi:10.1016/j.it.2013.08.004
- Derkach, V., Surprenant, A., & North, R.A. (1989). 5-HT<sub>3</sub> receptors are membrane ion channels. *Nature*, 339, 706–709. doi:10.1038/339706a0
- Domeney, A. M., Costall, B., Gerrard, P. A., Jones, D. N., Naylor, R. J., & Tyers, M.B. (1991). The effect of ondansetron on cognitive performance in the marmoset. *Pharmacology Biochemistry and Behavior*, 38, 169–175.
- Drews, J. (2000). Drug discovery: a historical perspective. *Science*, 287, 1960–1964.
- Dürk, T., Panther, E., Müller, T., Soricter, S., Ferrari, D., Pizzirani, C., ... Idzko, M. (2005). 5-Hydroxytryptamine modulates cytokine and chemokine production in LPS-primed human monocytes via stimulation of different 5-HTR subtypes. *International Immunology*, 17, 599–606. doi:10.1093/intimm/dxh242
- Egermayer, P., Town, G. I., & Peacock, A.J. (1999). Role of serotonin in the pathogenesis of acute and chronic pulmonary hypertension. *Thorax*, 54, 161–168.
- Filip, M., & Bader, M. (2009). Overview on 5-HT receptors and their role in physiology and pathology of the central nervous system. *Pharmacological Reports*, 61, 761–777.
- Franco-Molina, M., Gomez-Flores, R., Tamez-Guerra, P., Tamez-Guerra, R., Castillo-Leon, L., & Rodriguez-Padilla, C. (2003). In vitro immunopotentiating properties and tumour cell toxicity induced by *Lophophora williamsii* (peyote) cactus methanolic extract. *Phytotherapy Research*, 17, 1076–1081. doi:10.1002/ptr.1313
- Fredriksson, R., Lagerstrom, M. C., Lundin, L. G., & Schiöth, H.B. (2003). The G-protein-coupled receptors in the human genome form five main families. Phylogenetic analysis, paralogon groups, and fingerprints. *Molecular Pharmacology*, 63, 1256–1272. doi:10.1124/mol.63.6.1256
- Furtado, M., & Katzman, M.A. (2015). Examining the role of neuroinflammation in major depression. *Psychiatry Research*, 229, 27–36. doi:10.1016/j.psychres.2015.06.009
- Fuxe, K., Farnebo, L. O., Hamberger, B., & Ögren, S.O. (1975). On the in vivo and in vitro actions of fenfluramine and its derivatives on central monoamine neurons, especially 5-hydroxytryptamine neurons, and their relation to the anorectic activity of fenfluramine. *Postgraduate Medical Journal*, 51 Suppl, 1, 35–45.
- Ghia, J.-E., Li, N., Wang, H., Collins, M., Deng, Y., El-Sharkawy, R. T., ... Khan, W.I. (2009). Serotonin has a key role in pathogenesis of experimental colitis. *Gastroenterology*, 137, 1649–1660. doi:10.1053/j.gastro.2009.08.041
- Giulietti, M., Vivenzio, V., Piva, F., Principato, G., Bellantuono, C., & Nardi, B. (2014). How much do we know about the coupling of G-proteins to serotonin receptors? *Molecular Brain*, 7, 49. doi:10.1186/s13041-014-0049-y
- Godfrey, R. W., Lorimer, S., Majumdar, S., Adelroth, E., Johnston, P. W., Rogers, A. V., ... Jeffery, P.K. (1995). Airway and lung elastic fibre is not reduced in asthma nor in asthmatics following corticosteroid treatment. *European Respiratory Journal*, 8, 922–927.
- Gööz, M., Gööz, P., Luttrell, L. M., & Raymond, J.R. (2006). 5-HT<sub>2A</sub> receptor induces ERK phosphorylation and proliferation through ADAM-17 tumor necrosis factor- $\alpha$ -converting enzyme (TACE) activation and heparin-bound epidermal growth factor-like growth factor (HB-EGF) shedding in mesangial cells. *The Journal of Biological Chemistry*, 281, 21004–21012. doi:10.1074/jbc.M512096200
- Graham, J.R. (1964). Methysergide for prevention of headache; experience in five hundred patients over three years. *The New England Journal of Medicine*, 270, 67–72. doi:10.1056/nejm196401092700202

- Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., ... Klinedinst, M.A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology*, 30, 1181–1197. doi:10.1177/0269881116675513
- Gunawardhana, L. P., Gibson, P. G., Simpson, J. L., Powell, H., & Baines, K.J. (2014). Activity and expression of histone acetylases and deacetylases in inflammatory phenotypes of asthma. *Clinical and Experimental Allergy*, 44, 47–57. doi:10.1111/cea.12168
- Hamid, Q., & Tulic, M. (2009). Immunobiology of asthma. *Annual Review of Physiology*, 71, 489–507. doi:10.1146/annurev.physiol.010908.163200
- Harbuz, M. S., Marti, O., Lightman, S. L., & Jessop, D.S. (1998). Alteration of central serotonin modifies onset and severity of adjuvant-induced arthritis in the rat. *British Journal of Rheumatology*, 37, 1077–1083.
- Harbuz, M. S., Perveen-Gill, Z., Lallies, M. D., Jessop, D. S., Lightman, S. L., & Chowdrey, H.S. (1996). The role of endogenous serotonin in adjuvant-induced arthritis in the rat. *British Journal of Rheumatology*, 35, 112–116.
- Heffter, A. (1898). Ueber pellote. Beitrag zur chemischen und pharmakologischen kenntnis der cacteen. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 40, 385–429.
- Hekking, P. P., Wener, R. R., Amelink, M., Zwinderman, A. H., Bouvy, M. L., & Bel, E.H. (2015). The prevalence of severe refractory asthma. *The Journal of Allergy and Clinical Immunology*, 135, 896–902. doi:10.1016/j.jaci.2014.08.042
- Herr, N., Bode, C., & Duerschmied, D. (2017). The Effects of Serotonin in Immune Cells. *Frontiers in Cardiovascular Medicine*, 4, 48. doi:10.3389/fcvm.2017.00048
- Hey, P. (1947). The synthesis of a new homologue of mescaline. *Quarterly Journal of Pharmacy and Pharmacology*, 20, 129–134.
- Hill, A. S., Sahay, A., & Hen, R. (2015). Increasing Adult Hippocampal Neurogenesis is Sufficient to Reduce Anxiety and Depression-Like Behaviors. *Neuropsychopharmacology*, 40, 2368–2378. doi:10.1038/npp.2015.85
- Holloway, T., & Gonzalez-Maeso, J. (2015). Epigenetic Mechanisms of Serotonin Signaling. *ACS Chemical Neuroscience*, 6, 1099–1109. doi:10.1021/acschemneuro.5b00033
- Hong, H., Kim, B. S., & Im, H.I. (2016). Pathophysiological role of neuroinflammation in neurodegenerative diseases and psychiatric disorders. *International Neuropsychology Journal*, 20, S2–S7. doi:10.5213/inj.1632604.302
- Hoyer, D., Clarke, D. E., Fozard, J. R., Hartig, P. R., Martin, G. R., Mylecharane, E. J., ... Humphrey, P.P. (1994). International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (Serotonin). *Pharmacological Reviews*, 46, 157–203.
- Inoue, M., Okazaki, T., Kitazono, T., Mizushima, M., Omata, M., & Ozaki, S. (2011). Regulation of antigen-specific CTL and Th1 cell activation through 5-Hydroxytryptamine 2A receptor. *International Immunopharmacology*, 11, 67–73. doi:10.1016/j.intimp.2010.10.007
- Ito, K., Caramori, G., Lim, S., Oates, T., Chung, K. F., Barnes, P. J., & Adcock, I.M. (2002). Expression and activity of histone deacetylases in human asthmatic airways. *American Journal of Respiratory and Critical Care Medicine*, 166, 392–396. doi:10.1164/rccm.2110060
- Ito, T., Ikeda, U., Shimpō, M., Yamamoto, K., & Shimada, K. (2000). Serotonin increases interleukin-6 synthesis in human vascular smooth muscle cells. *Circulation*, 102, 2522–2527.
- Janeway, C.A.J.T.P., Walport, M., & Shlomchik, M. (2001). *The Immune System in Health and Disease*, (5th ed.). New York: New Garland Science.
- Jeffery, P. K., Godfrey, R. W., Adelroth, E., Nelson, F., Rogers, A., & Johansson, S.A. (1992). Effects of treatment on airway inflammation and thickening of basement membrane reticular collagen in asthma. A quantitative light and electron microscopic study. *The American Review of Respiratory Disease*, 145, 890–899. doi:10.1164/ajrccm/145.4\_Pt\_1.890
- Johnson, M. P., Hoffman, A. J., Nichols, D. E., & Mathis, C.A. (1987). Binding to the serotonin 5-HT<sub>2</sub> receptor by the enantiomers of 125I-DOI. *Neuropharmacology*, 26, 1803–1806.
- Jouvet, M., Bobillier, P., Pujol, J. F., & Renault, J. (1967). [Suppression of sleep and decrease of cerebral serotonin caused by lesion of the raphe system in the cat]. *Comptes rendus de l'Académie des Sciences*, 264, 360–362.
- Kang, B. N., Ha, S. G., Bahaie, N. S., Hosseinkhani, M. R., Ge, X. N., Blumenthal, M. N., ... Sriram Rao, P. (2013). Regulation of serotonin-induced trafficking and migration of eosinophils. *PLoS One*, 8, e54840. doi:10.1371/journal.pone.0054840
- Kenakin, T. (2010). A holistic view of GPCR signaling. *Nature Biotechnology*, 28, 928–929. doi:10.1038/nbt0910-928
- Kenakin, T. (2011). Functional selectivity and biased receptor signaling. *Journal of Pharmacology and Experimental Therapeutics*, 336, 296–302. doi:10.1124/jpet.110.173948
- Khan, W.I. (2013). The role of 5-HT dysregulation in inflammatory bowel disease. *Gastroenterology and Hepatology*, 9, 259–261.
- Kim, H. Y., DeKruyff, R. H., & Umetsu, D.T. (2010). The many paths to asthma: phenotype shaped by innate and adaptive immunity. *Nature Immunology*, 11, 577–584. doi:10.1038/ni.1892
- Kubera, M., Maes, M., Kenis, G., Kim, Y.-K., & Lasoń, W. (2005). Effects of serotonin and serotonergic agonists and antagonists on the production of tumor necrosis factor alpha and interleukin-6. *Psychiatry Research*, 134, 251–258. doi:10.1016/j.psychres.2004.01.014
- Kyzar, E. J., Nichols, C. D., Gainetdinov, R. R., Nichols, D. E., & Kalueff, A.V. (2017). Psychedelic drugs in biomedicine. *Trends in Pharmacological Sciences*, 38, 992–1005. doi:10.1016/j.tips.2017.08.003
- Laguzzi, R., Reis, D. J., & Talman, W.T. (1984). Modulation of cardiovascular and electrocortical activity through serotonergic mechanisms in the nucleus *Tractus solitarius* of the rat. *Brain Research*, 304, 321–328.
- Leon-Ponte, M., Ahern, G. P., & O'Connell, P.J. (2007). Serotonin provides an accessory signal to enhance T-cell activation by signaling through the 5-HT<sub>7</sub> receptor. *Blood*, 109, 3139–3146. doi:10.1182/blood-2006-10-052787

- Locke, N. R., Royce, S. G., Wainwright, J. S., Samuel, C. S., & Tang, M.L. (2007). Comparison of airway remodeling in acute, subacute, and chronic models of allergic airways disease. *American Journal of Respiratory Cell and Molecular Biology*, 36, 625–632. doi:10.1165/rcmb.2006-0083OC
- Mabry, P. D., & Campbell, B.A. (1973). Serotonergic inhibition of catecholamine-induced behavioral arousal. *Brain Research*, 49, 381–391.
- Marconi, A., Darquenne, S., Boulmerka, A., Mosnier, M., & D'Alessio, P. (2003). Naftidrofuryl-driven regulation of endothelial ICAM-1 involves nitric oxide. *Free Radical Biology and Medicine*, 34, 616–625.
- Margolis, K. G., Stevanovic, K., Li, Z., Yang, Q. M., Oravec, T., Zambrowicz, B., ... Gershon, M.D. (2014). Pharmacological reduction of mucosal but not neuronal serotonin opposes inflammation in mouse intestine. *Gut*, 63, 928–937. doi:10.1136/gutjnl-2013-304901
- Mason, J. S., Bortolato, A., Congreve, M., & Marshall, F.H. (2012). New insights from structural biology into the druggability of G protein-coupled receptors. *Trends in Pharmacological Sciences*, 33, 249–260. doi:10.1016/j.tips.2012.02.005
- McAlear, S. D., Kraft, T. W., & Gross, A.K. (2010). 1 rhodopsin mutations in congenital night blindness. *Advances in Experimental Medicine and Biology*, 664, 263–272. doi:10.1007/978-1-4419-1399-9\_30
- McBride, P. A., Mann, J. J., McEwen, B., & Biegon, A. (1983). Characterization of serotonin binding sites on human platelets. *Life Sciences*, 33, 2033–2041.
- McCorvy, J. D., & Roth, B.L. (2015). Structure and function of serotonin G protein-coupled receptors. *Pharmacology and Therapeutics*, 150, 129–142. doi:10.1016/j.pharmthera.2015.01.009
- McKenna, D. J., Nazarali, A. J., Hoffman, A. J., Nichols, D. E., Mathis, C. A., & Saavedra, J.M. (1989). Common receptors for hallucinogens in rat brain: a comparative autoradiographic study using [125I]LSD and [125I]DOI, a new psychotomimetic radioligand. *Brain Research*, 476, 45–56.
- McKune, C. M., & Watts, S.W. (2001). Characterization of the serotonin receptor mediating contraction in the mouse thoracic aorta and signal pathway coupling. *Journal of Pharmacology and Experimental Therapeutics*, 297, 88–95.
- Medzhitov, R. (2008). Origin and physiological roles of inflammation. *Nature*, 454, 428–435. doi:10.1038/nature07201
- Meltzer, H.Y. (1995). Role of serotonin in the action of atypical antipsychotic drugs. *Journal of Clinical Neuroscience*, 3, 64–75.
- Meyerson, B. J., & Lewander, T. (1970). Serotonin synthesis inhibition and estrous behavior in female rats. *Life Science I*, 9, 661–671.
- Mikulski, Z., Zasłona, Z., Cakarova, L., Hartmann, P., Wilhelm, J., Tecott, L. H., ... Kummer, W. (2010). Serotonin activates murine alveolar macrophages through 5-HT<sub>2C</sub> receptors. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, 299, L272–L280. doi:10.1152/ajplung.00032.2010
- Miller, K. J., & Gonzalez, H.A. (1998). Serotonin 5-HT<sub>2A</sub> receptor activation inhibits cytokine-stimulated inducible nitric oxide synthase in C6 glioma cells. *Annals of the New York Academy of Sciences*, 861, 169–173.
- Miller, K. J., Mariano, C. L., & Cruz, W.R. (1997). Serotonin 5HT<sub>2A</sub> receptor activation inhibits inducible nitric oxide synthase activity in C6 glioma cells. *Life Science*, 61, 1819–1827.
- Moore, A. R., Ceraudo, E., Sher, J. J., Guan, Y., Shoushtari, A. N., Chang, M. T., ... Chen, Y. (2016). Recurrent activating mutations of G-protein-coupled receptor CYSLTR2 in uveal melanoma. *Nature Genetics*, 48, 675–680. doi:10.1038/ng.3549
- Morales-García, J. A., de la Fuente Revenga, M., Alonso-Gil, S., Rodríguez-Franco, M. I., Feilding, A., Perez-Castillo, A., & Riba, J. (2017). The alkaloids of Banisteriopsis caapi, the plant source of the Amazonian hallucinogen Ayahuasca, stimulate adult neurogenesis in vitro. *Scientific Reports*, 7, 5309. doi:10.1038/s41598-017-05407-9
- Moreira, A. P., & Hogaboam, C.M. (2011). Macrophages in allergic asthma: fine-tuning their pro- and anti-inflammatory actions for disease resolution. *Journal of Interferon and Cytokine Research*, 31, 485–491. doi:10.1089/jir.2011.0027
- Nagatomo, T., Rashid, M., Abul Muntasir, H., & Komiyama, T. (2004). Functions of 5-HT<sub>2A</sub> receptor and its antagonists in the cardiovascular system. *Pharmacology and Therapeutics*, 104, 59–81. doi:10.1016/j.pharmthera.2004.08.005
- Naik, S. R., & Wala, S.M. (2013). Inflammation, allergy and asthma, complex immune origin diseases: mechanisms and therapeutic agents. *Recent Patents on Inflammation and Allergy Drug Discovery*, 7, 62–95.
- Najjar, S., Pearlman, D. M., Alper, K., Najjar, A., & Devinsky, O. (2013). Neuroinflammation and psychiatric illness. *Journal of Neuroinflammation*, 10, 43. doi:10.1186/1742-2094-10-43
- Nakae, S., Lunderius, C., Ho, L. H., Schafer, B., Tsai, M., & Galli, S.J. (2007). TNF can contribute to multiple features of ovalbumin-induced allergic inflammation of the airways in mice. *Journal of Allergy and Clinical Immunology*, 119, 680–686. doi:10.1016/j.jaci.2006.11.701
- Nau, F., Miller, J., Saravia, J., Ahlert, T., Yu, B., Happel, K. I., ... Nichols, C.D. (2015). Serotonin 5-HT<sub>2</sub> receptor activation prevents allergic asthma in a mouse model. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, 308, L191–L198. doi:10.1152/ajplung.00138.2013
- Nau, F., Jr., Yu, B., Martin, D., & Nichols, C.D. (2013). Serotonin 5-HT<sub>2A</sub> receptor activation blocks TNF-alpha mediated inflammation in vivo. *PLoS One*, 8, e75426. doi:10.1371/journal.pone.0075426
- Nichols, C.D. (2009). Serotonin 5-HT<sub>2A</sub> receptor function as a contributing factor to both neuropsychiatric and cardiovascular diseases. *Cardiovascular Psychiatry and Neurology*, 2009, 1. doi:10.1155/2009/475108
- Nichols, D.E. (2012). Structure-activity relationships of serotonin 5-HT<sub>2A</sub> agonists. *WIREs Membrane Transport and Signaling*, 1, 559–579.
- Nichols, D.E. (2016). Psychedelics. *Pharmacological Reviews*, 68, 264–355. doi:10.1124/pr.115.011478
- Nichols, D. E., Johnson, M. W., & Nichols, C.D. (2017). Psychedelics as Medicines: An Emerging New Paradigm.

- Clinical Pharmacology & Therapeutics*, 101, 209–219. doi:10.1002/cpt.557
- Nichols, D. E., & Nichols, C.D. (2008). Serotonin receptors. *Chemical Reviews*, 108, 1614–1641. doi:10.1021/cr078224o
- Nocito, A., Dahm, F., Jochum, W., Jang, J. H., Georgiev, P., Bader, M., ... Clavien, P.-A. (2007). Serotonin mediates oxidative stress and mitochondrial toxicity in a murine model of nonalcoholic steatohepatitis. *Gastroenterology*, 133, 608–618. doi:10.1053/j.gastro.2007.05.019
- Osmond, H. (1957). A review of the clinical effects of psychotomimetic agents. *Annals of the New York Academy of Sciences*, 66, 418–434.
- Overington, J. P., Al-Lazikani, B., & Hopkins, A.L. (2006). How many drug targets are there? *Nature Reviews Drug Discovery*, 5, 993–996. doi:10.1038/nrd2199
- Palczewski, K., Kumasaka, T., Hori, T., Behnke, C. A., Motoshima, H., Fox, B. A., ... Miyano, M., (2000). Crystal structure of rhodopsin: A G protein-coupled receptor. *Science*, 2, 739–745.
- Pellegrino, T. C., & Bayer, B.M. (2002). Role of central 5-HT(2) receptors in fluoxetine-induced decreases in T lymphocyte activity. *Brain, Behavior, and Immunity*, 16, 87–103. doi:10.1006/brbi.2001.0625
- Pelletier, M., & Siegel, R.M. (2009). Wishing away inflammation? New links between serotonin and TNF signaling. *Molecular Interventions*, 9, 299–301. doi:10.1124/mi.9.6.5
- Peretz, D. I., Smythies, J. R., & Gibson, W.C. (1955). A new hallucinogen: 3,4,5-trimethoxyphenyl-beta-aminopropane with notes on the stroboscopic phenomenon. *The Journal of Mental Science*, 101, 317–329.
- Pierce, P. A., Xie, G. X., Peroutka, S. J., Green, P. G., & Levine, J.D. (1995). 5-Hydroxytryptamine-induced synovial plasma extravasation is mediated via 5-hydroxytryptamine<sub>2A</sub> receptors on sympathetic efferent terminals. *Journal of Pharmacology and Experimental Therapeutics*, 275, 502–508.
- Politis, M., & Loane, C. (2011). Serotonergic dysfunction in Parkinson's disease and its relevance to disability. *ScientificWorldJournal*, 11, 1726–1734. doi:10.1100/2011/172893
- Quirce, S., Phillips-Angles, E., Dominguez-Ortega, J., & Barranco, P. (2017). Biologics in the treatment of severe asthma. *Allergologia et Immunopathologia*, 45, 45–49. doi:10.1016/j.aller.2017.09.012
- Radtke, F. A., Chapman, G., Hall, J., & Syed, Y.A. (2017). Modulating Neuroinflammation to Treat Neuropsychiatric Disorders. *BioMed Research International*, 2017, 1. doi:10.1155/2017/5071786
- Ray, R. S., Corcoran, A. E., Brust, R. D., Kim, J. C., Richerson, G. B., Nattie, E., & Dymecki, S.M. (2011). Impaired respiratory and body temperature control upon acute serotonergic neuron inhibition. *Science*, 333, 637–642. doi:10.1126/science.1205295
- Raymond, J. R., Mukhin, Y. V., Gelasco, A., Turner, J., Collinsworth, G., Gettys, T. W., ... Garnovskaya, M.N. (2001). Multiplicity of mechanisms of serotonin receptor signal transduction. *Pharmacology and Therapeutics*, 92, 179–212.
- Ren, Y., Su, X., Kong, L., Li, M., Zhao, X., Yu, N., & Kang, J. (2016). Therapeutic effects of histone deacetylase inhibitors in a murine asthma model. *Inflammation Research*, 65, 995–1008. doi:10.1007/s00011-016-0984-4
- Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., ... Schmidt, B.L. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *Journal of Psychopharmacology*, 30, 1165–1180. doi:10.1177/0269881116675512
- Rossi, S., Studer, V., Motta, C., Polidoro, S., Perugini, J., Macchiarulo, G., ... Centonze, D. (2017). Neuroinflammation drives anxiety and depression in relapsing-remitting multiple sclerosis. *Neurology*, 89, 1338–1347. doi:10.1212/wnl.0000000000004411
- Roth, B. L., Berry, S. A., Kroeze, W. K., Willins, D. L., & Kristiansen, K. (1998). Serotonin 5-HT<sub>2A</sub> receptors: molecular biology and mechanisms of regulation. *Critical Reviews in Neurobiology*, 12, 319–338.
- Roth, B. L., & Kroeze, W.K. (2015). Integrated Approaches for Genome-wide Interrogation of the Druggable Non-olfactory G Protein-coupled Receptor Superfamily. *The Journal of Biological Chemistry*, 290, 19471–19477. doi:10.1074/jbc.R115.654764
- Ruddell, R. G., Oakley, F., Hussain, Z., Yeung, I., Bryan-Lluka, L. J., Ramm, G. A., & Mann, D.A. (2006). A role for serotonin (5-HT) in hepatic stellate cell function and liver fibrosis. *The American Journal of Pathology*, 169, 861–876. doi:10.2353/ajpath.2006.050767
- Samson, M., Libert, F., Doranz, B. J., Rucker, J., Liesnard, C., Farber, C.-M., ... Parmentier, M. (1996). Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. *Nature*, 382, 722–725. doi:10.1038/382722a0
- Shah, A. (2012). The pathologic and clinical intersection of atopic and autoimmune disease. *Curr Allergy Asthma Rep*, 12, 520–529. doi:10.1007/s11882-012-0293-0
- Shajib, M. S., & Khan, W.I. (2015). The role of serotonin and its receptors in activation of immune responses and inflammation. *Acta Physiologica*, 213, 561–574. (Oxf), doi:10.1111/apha.12430
- Shulgin, A. T., Sargent, T., & Naranjo, C. (1969). Structure-activity relationships of one-ring psychotomimetics. *Nature*, 221, 537–541.
- Shulgin, A., T., S., A. (1991). *PIHKAL: A Chemical Love Story*. Berkeley, CA: Transform Press.
- Smith, R. L., Barrett, R. J., & Sanders-Bush, E. (2003). Discriminative stimulus properties of 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane [(+/-)DOI] in C57BL/6J mice. *Psychopharmacology (Berl)*, 166, 61–68. doi:10.1007/s00213-002-1252-6
- Soga, F., Katoh, N., Inoue, T., & Kishimoto, S. (2007). Serotonin activates human monocytes and prevents apoptosis. *J Invest Dermatol*, 127, 1947–1955. doi:10.1038/sj.jid.5700824
- Sonda, S., Silva, A. B., Grabliauskaite, K., Saponara, E., Weber, A., Jang, J.-H., ... Graf, R. (2013). Serotonin regulates amylase secretion and acinar cell damage during murine pancreatitis. *Gut*, 62, 890–898. doi:10.1136/gutjnl-2011-301724
- Sonier, B., Lavigne, C., Arseneault, M., Ouellette, R., & Vaillancourt, C. (2005). Expression of the 5-HT<sub>2A</sub> serotonergic receptor in human placenta and choriocarcinoma cells: mitogenic implications of serotonin. *Placenta*, 26, 484–490. doi:10.1016/j.placenta.2004.08.003

- Sparkes, C. G., & Spencer, P.S. (1971). Antinociceptive activity of morphine after injection of biogenic amines in the cerebral ventricles of the conscious rat. *Br J Pharmacol*, 42, 230–241.
- Stefulj, J., Jernej, B., Cicin-Sain, L., Rinner, I., & Schauenstein, K. (2000). mRNA expression of serotonin receptors in cells of the immune tissues of the rat. *Brain Behav Immun*, 14, 219–224. doi:10.1006/brbi.1999.0579
- Steyn, M. E., Viljoen, M., Ubbink, J. B., van Rensburg, B. W., & Reinach, S.G. (1992). Whole blood serotonin levels in chronic renal failure. *Life Sci*, 51, 359–366.
- Strawbridge, R., Arnone, D., Danese, A., Papadopoulos, A., Herane Vives, A., & Cleare, A.J. (2015). Inflammation and clinical response to treatment in depression: A meta-analysis. *Eur Neuropsychopharmacol*, 25, 1532–1543. doi:10.1016/j.euroneuro.2015.06.007
- Thiebot, M.H. (1986). Are serotonergic neurons involved in the control of anxiety and in the anxiolytic activity of benzodiazepines? *Pharmacology Biochemistry and Behavior*, 24, 1471–1477.
- Urban, J. D., Clarke, W. P., von Zastrow, M., Nichols, D. E., Kobilka, B., Weinstein, H., ... Mailman, R.B. (2007). Functional selectivity and classical concepts of quantitative pharmacology. *Journal of Pharmacology and Experimental Therapeutics*, 320, 1–13. doi:10.1124/jpet.106.104463
- Vollenweider, F. X., Vollenweider-Scherpenhuyzen, M. F., Babler, A., Vogel, H., & Hell, D. (1998). Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *Neuroreport*, 9, 3897–3902.
- Wacker, D., Stevens, R. C., & Roth, B.L. (2017). How Ligands Illuminate GPCR Molecular Pharmacology. *Cell*, 170, 414–427. doi:10.1016/j.cell.2017.07.009
- Warrington, R., Watson, W., Kim, H. L., & Antonetti, F.R. (2011). An introduction to immunology and immunopathology. *Allergy, Asthma & Clinical Immunology*, 7, S1. doi:10.1186/1710-1492-7-s1-s1
- Welsh, D. J., Harnett, M., MacLean, M., & Peacock, A.J. (2004). Proliferation and signaling in fibroblasts: role of 5-hydroxytryptamine<sub>2A</sub> receptor and transporter. *American Journal of Respiratory and Critical Care Medicine*, 170, 252–259. doi:10.1164/rccm.200302-264OC
- Williams, G. V., Rao, S. G., & Goldman-Rakic, P.S. (2002). The physiological role of 5-HT<sub>2A</sub> receptors in working memory. *Journal of Neuroscience* 22, 2843–2854. doi:20026203
- Yu, B., Becnel, J., Zerfaoui, M., Rohatgi, R., Boulares, A. H., & Nichols, C.D. (2008). Serotonin 5-hydroxytryptamine(2A) receptor activation suppresses tumor necrosis factor-alpha-induced inflammation with extraordinary potency. *Journal of Pharmacology and Experimental Therapeutics*, 327, 316–323. doi:10.1124/jpet.108.143461