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REVIEW ARTICLE

Are we hallucinating or can psychedelic drugs modulate the immune system to control inflammation?

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Psychedelic drugs that activate 5-HT_{2A} receptors have been long used for cultural, medicinal and recreational purposes. Interest in psychedelics for treating psychiatric disorders has resurged recently and is well documented; less well recognised are their anti-inflammatory properties. Growing evidence now demonstrates that psychedelics modulate immune responses, including inhibiting pro-inflammatory cytokine release. Furthermore, in vivo studies demonstrate that psychedelics, like (*R*)-DOI, reduce inflammation in animal models of acute and chronic inflammatory disease such as asthma. Likewise, some clinical studies with psychedelic drugs (e.g. psilocybin) demonstrate an impact upon circulating cytokine levels, supporting a translation from the animal models to the clinical arena. Such data emphasise the promise of therapeutic approaches targeting inflammation. Interestingly, recent research has also uncovered compounds that maintain therapeutic potential without likely causing psychedelic effects. These discoveries suggest that drugs informed by psychedelic drugs, but which do not evoke psychedelic experiences, which we term PIPI drugs (Psychedelic drug Informed but Psychedelic experience Inactive), could offer effective treatments for mental health and inflammation, presenting new avenues for therapeutic development.

KEYWORDS
5-HT2A receptor, immune system, inflammation, neuroinflammation, psychedelic drugs

Abbreviations: CRP, C-reactive protein; CXCL, chemokine (C-X-C motif) ligand; (*R*)-DOTFM, (*R*)-2,5-dimethoxy-4-trifluoromethylamphetamine; EEG, electroencephalogram; GM-CSF, granulocyte-macrophage colony-stimulating factor; HTR, head twitch response; IBG, ibogaine; IFN, interferon; MAD, multiple ascending dose; MCP, monocyte chemo-attractant protein; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; moDC, monocyte-derived dendritic cells; NFAT, nuclear factor of activated T-cells; OVA, ovalbumin; PIPI, psychedelic drug informed but psychedelic experience inactive; SAD, single ascending dose; TBG, tabernanthalog; TGFβ, transforming growth factor β.

1 | INTRODUCTION

1.1 | Discovery of psychedelics

Organic molecules possessing psychedelic[1] activity are found in various fungi, plants and animals. Synthesis of these molecules may have evolved to evoke confusion in foraging animals in an attempt to avert repeat sampling and, hence, avoid the destruction of the respective flora and fauna (Alrashedy & Molina, 2016). In an ironic twist, for millennia, these very pharmacological actions have encouraged human ingestion for hedonistic experiences, cultural rituals and medicinal purposes and perhaps ingestion by other animals also for the experience (e.g. Haynes, 2010; Rodríguez Arce & Arce Cerdas, 2019; Samorini, 2019; Winkelman, 2019).

The dawning of modern pharmacology associated with psychedelic drugs is often attributed to the work of Albert Hofmann with his synthesis of lysergic acid diethylamide (**LSD**) in 1938. Interestingly, at the time, this 'no special interest' molecule was side-lined for 5 years before being plucked from obscurity, leading to Hofmann's legendary psychedelic experiences on a cycle ride home (Hoffmann, 1980). The subsequent explosion in research aimed at understanding the pharmacological actions of psychedelics occurred alongside the rise in their misuse by those seeking psychedelic experiences, which peaked in the 1960s with the so-called 'flower power' movement. Alarmed by this perceived deviant behaviour and concerned by the supposed detrimental effect upon orderly society, governments around the World introduced legislation criminalising their use, resulting in the desired dramatic decline in recreational use. Unfortunately, this legislation also severely limited legitimate research on psychedelics for several decades, with only a few pioneers continuing to explore their actions and mechanisms. For more detail around the historical investigation of activity and use of psychedelic drugs, please see these excellent reviews (Carhart & Goodwin, 2017; Kyzar et al., 2017).

In the last decade, there has been a resurgence of interest in the therapeutic potential of psychedelic drugs. This interest is at least partly fuelled by the remaining clear unmet medical need for better treatments for depression, anxiety and some other psychiatric disorders. Thus, for instance, while improvements have been made in options for anti-depressant medication (Cipriani et al., 2018), still only a minority of patients gain substantial benefit and often only after a troublesome delay of a few weeks before the onset of symptomatic relief. Against this background, the potential of psychedelic drugs and derivatives that may possess improved benefit: risk ratios has spurred numerous commercial enterprises keen to exploit the therapeutic potential for the benefit of patients and the subsequent commercial return for their stakeholders and investors. Initially, the investigated indications were centred around depression and anxiety (Carhart-Harris et al., 2021; Griffiths et al., 2016; Holze et al., 2023; Reckweg et al., 2023; Ross et al., 2016), but this has now expanded to conditions such as post-traumatic stress disorder, substance abuse disorder and pain (Kooijman et al., 2023; Robinson et al., 2024). There is also a growing interest from evidence that patients with inflammatory conditions may gain clinical benefit from drugs mimicking some of the pharmacological actions of psychedelic drugs. Indeed, there may be common underlying mechanisms between inflammatory and psychiatric disorders because low-grade inflammation is associated with sub-populations of patients with various psychiatric conditions, including depression and psychosis (e.g. Lalousis et al., 2024; Osimo et al., 2020; Upthegrove et al., 2014; Williams et al., 2022).

While the detailed cellular and molecular mechanisms underlying the recreational and potential therapeutic actions of psychedelic drugs are far from understood (but see Gumpper et al., 2025), the ability of psychedelic drugs to reduce mediators of inflammation is beginning to be appreciated. Clear definitive results following independent replication with comparable protocols are still needed. The present review focusses on the anti-inflammatory actions of psychedelic drugs and the potential of non-psychedelic drugs arising from psychedelic drug research. The included drugs all engage the primary molecular target responsible for psychedelic activity, namely the **5-HT$_{2A}$** receptor (e.g. Halberstadt et al., 2020; Madsen et al., 2019; Preller et al., 2017; for reviews see Halberstadt, 2015; Sharp & Barnes, 2020), although not all the drugs are 5-HT$_{2A}$ receptor selective.

1.2 | Evidence for anti-inflammatory actions of psychedelic drugs using human cells

The most consistent reported impact of psychedelic drugs upon a human immune cell subset is the inhibition of stimulated tumour necrosis factor α (TNFα) release from monocytes in vitro (Figure 1); monocytes are key innate immune cells that release a range of cytokines and chemokines upon stimulation, including the pro-inflammatory cytokine, TNFα. Monocyte function is altered in a number of inflammatory diseases. For instance, monocytes from patients with either rheumatoid arthritis or multiple sclerosis exhibit increased production of TNFα compared to healthy controls (Filion et al., 2003; Leirisalo-Repo et al., 1995). During acute and chronic inflammation, monocytes may migrate from the blood into tissues and differentiate into monocyte-derived macrophages or monocyte-derived dendritic cells (Villar et al., 2023). TNFα plays critical functional roles in orchestrating inflammatory responses and its neutralisation brings therapeutic benefit in inflammatory diseases such as rheumatoid arthritis (for review, see Feldman, 2002) and inflammatory bowel disease (for review see Sandborn & Hanauer, 1999). Modulation of monocyte TNFα release by psychedelics therefore reveals one of their anti-inflammatory actions. For example, the psychedelic drug, 2,5-dimethoxy-4-iodoamphetamine (**(R)-DOI**), which displays some selectivity as a 5-HT$_{2A}$ receptor agonist (Barnes et al., 2021), inhibits acute stimulated TNFα release from isolated monocytes. Similarly, (*R*)-DOI inhibits TNFα release from a peripheral blood mononuclear cell (PBMC) mix stimulated with a toll-like receptor 4 (**TLR4**) receptor agonist (lipopolysaccharide [**LPS**]), which results predominantly in the activation of monocytes within the PBMC mix. The endogenous

[1]Drugs that evoke LSD-like psychedelic experiences (e.g. induce hallucinatory or altered state of consciousness) in humans activate the 5-HT$_{2A}$ receptor (Gumpper & Roth, 2024).

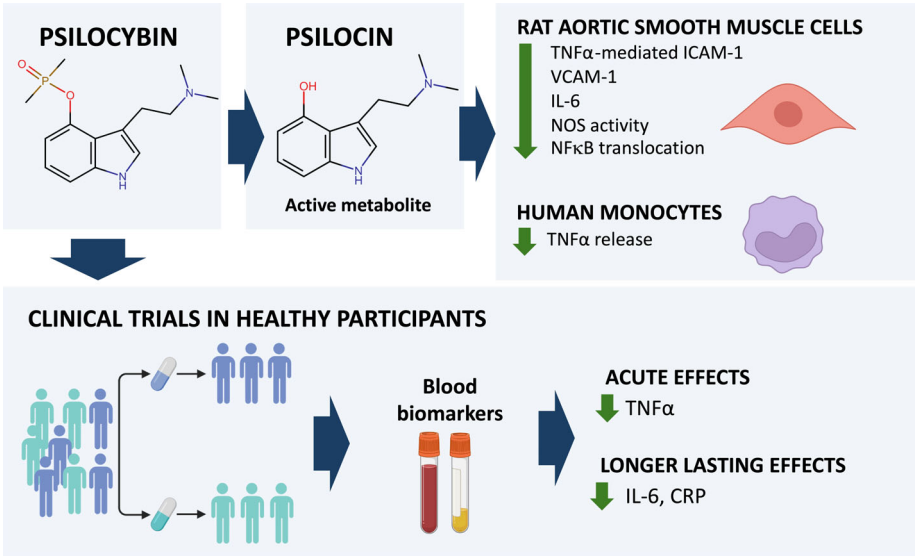

FIGURE 1 Anti-inflammatory actions of the psychedelic drug, psilocybin, in clinical trial and impact of the active metabolite, psilocin, upon isolated cells in vitro.

agonist **5-HT** mimics the impact of (*R*)-DOI upon monocytes and LPS-stimulated PBMCs (Cloëz-Tayarani et al., 2003; Dürk et al., 2005). Because, ketanserin, the somewhat selective 5-HT_{2A} receptor antagonist (Barnes et al., 2021), blocks these responses at relevant concentrations, this further supports a role for the 5-HT_{2A} receptor, which is expressed at mRNA and protein levels in these cells (both non-stimulated and LPS-stimulated monocytes; Cloëz-Tayarani et al., 2003). It should be noted, however, that the 5-HT receptor inhibiting the release of TNFα from human monocytes (both resting and LPS-stimulated) may be questioned by the results from a different in vitro study where micromolar concentrations of 5-HT were effective, yet (*R*)-DOI at a wide range of concentrations (0.1 μM to 1.0 mM; i.e. near- and supra-maximal concentrations to activate the 5-HT_{2A} receptor) was essentially inactive (Dürk et al., 2005), although 5-HT_{2A} receptor expression by the monocytes in the study was evident. However, the 5-HT response was emulated by high micromolar concentrations of 2-methoxytryptamine and **8-OH-DPAT**. While both these latter compounds engage the human 5-HT_{2A} receptor at micromolar concentrations (Knight et al., 2004), the ability of these agonist responses in this model to be blocked by relevant concentrations of the selective **5-HT_4 receptor** antagonist, RS-39604, and the **5-HT_7 receptor** antagonists, SB-269970 and pimozide, as well as the **adenylate cyclase** inhibitor, MDL-12330A, suggests involvement of 5-$HT_{4/7}$ receptors, rather than 5-HT_{2A} receptors, in this model. The lack of action of (*R*)-DOI in this model of TNFα release from human monocytes emphasises a clear difference to results from some other studies.

Another human immune cell type that appears to be impacted by psychedelic drugs are dendritic cells which, like monocytes, are members of the mononuclear phagocyte system. These cells bridge the innate and the adaptive arms of the immune system and, while they may be differentiated from monocytes during inflammation, are derived from distinct haematopoietic stem cell precursors from those of monocytes and macrophages (for review, see Guilliams et al., 2015). Dendritic cells phagocytose and process antigenic material into shorter antigenic matter to then be presented as an MHC–peptide complex on the dendritic cell surface to other immune cells, where for instance they potently activate responsive T cells to promote adaptive immune responses (Steinman & Witmer, 1978). In addition, activation of dendritic cells by antigenic material also evokes the release of, for example, cytokines to provide a humoral propagation of the immune response. It is well established that peripheral blood monocytes can be differentiated in vitro to generate cells resembling dendritic cells (monocyte-derived dendritic cells; moDC). Szabo et al. (2014) used this latter approach to demonstrate the action of two psychedelic molecules, N,N-dimethyltryptamine (**DMT**) and 5-methoxy-N,N-dimethyltryptamine (**5-MeO-DMT**), upon human moDCs. Both molecules, in a concentration-dependent manner, inhibited TNFα release from either LPS or poly I:C (the latter a **TLR3** receptor agonist that mimics double-stranded viral RNA) stimulated moDCs. A maximal—albeit high—concentration of each psychedelic molecule (100 μM) also inhibited the expression (mRNA) and release of the pro-inflammatory cytokines, interleukin-1β (IL-1β), **IL-6** and IL-8, and to further tip the balance towards an anti-inflammatory response, the psychedelic molecules also increased the expression (mRNA) and release of the generally considered anti-inflammatory cytokine, IL-10.

As well as an impact upon cytokine release from dendritic cells, Szabo and colleagues' study (2014) also demonstrated that both psychedelic molecules (DMT and 5-MeO-DMT, again, each at the high concentration of 100 μM) inhibited the antigen presentation function of moDCs (fed either heat-killed *Escherichia coli* or inactivated influenza virus) evident from their reduced ability to activate autologous pro-inflammatory T cells resulting in a lower release of the pro-inflammatory cytokines, IFNγ (i.e. by Th1 cells) or IL-17 (i.e. by Th17 cells). The pharmacology of the responses evoked by the two psychedelic molecules would appear complicated, however. Thus, while both molecules are 5-HT_{2A} receptor ligands (Roth et al., 2000) and DMT is a partial agonist at the recombinant h5-HT_{2A} receptor (around 40% intrinsic activity to evoke generation of the second messenger, IP1; Janowsky et al., 2014), Szabo et al. (2014) present evidence that the responses

arise, at least in part, via engagement of the **σ-1 receptor** because siRNA gene silencing of this receptor inhibited around 50% of the responses evoked by the psychedelic molecules. Furthermore, the selective σ−1 receptor agonist, PRE-084 (Su et al., 1991), mimicked the action of the psychedelic molecules on TNFα and IL-10 release from the moDCs, yet here the gene silencing strategy inhibited the response completely. Therefore, the only *partial* block of the responses evoked by the psychedelic drugs following σ−1 receptor-gene silencing suggests an additional pharmacological mechanism may have been active, with the 5-HT_{2A} receptor a likely candidate. It would be interesting to assess the impact of a 5-HT_{2A} receptor antagonist on the responses to these high concentrations of DMT and 5-MeO-DMT to determine if there was indeed a contribution from the 5-HT_{2A} receptor.

Hence, in general, while there is intriguing evidence for psychedelic drugs to inhibit the release of pro-inflammatory mediators, there are inconsistencies that, along with the use of related but different cell types, may also be attributed to the variation often evident using human primary cells from different donors. The discrepancies when comparing the pharmacology of human systems to those in rodents might also contribute to variation. While studies often report on 5-HT_{2A} receptor expression in human monocytes, immune cell subsets, in general, exhibit low levels of 5-HT_{2A} receptor expression in human expression maps.[2] These maps tend to report the expression by cells in their resting states, which is unlikely to represent their phenotype in inflammatory disease; hence, a more detailed investigation of 5-HT_{2A} receptor expression by immune cell subsets in pathological inflammatory conditions is warranted. One further cell type worthy of detailed investigation is microglia, the resident macrophages in the human brain, which promote neuroinflammatory responses in, for example, traumatic brain injury (for reviews, see Donat et al., 2017; Wangler & Godbout, 2023), for which there is also a dire need for pharmacological treatments.

1.3 | Evidence for anti-inflammatory actions of psychedelic drugs using animals: in vitro and in vivo studies

Pioneering work from Charles Nichols' laboratory has identified anti-inflammatory actions of psychedelic drugs both in vitro and in vivo. The in vitro work has used rat aortic smooth muscle cells to demonstrate that a range of psychedelic drugs, including (*R*)-DOI, suppress expression of pro-inflammatory molecules (e.g. the cytokine IL-6 and the integrin ligands, **ICAM-1** and **VCAM-1**; Figure 1). Additionally, (*R*)-DOI reduced the activation and translocation of the inducible transcription factor, NF-κB p65 (Yu et al., 2008), which is known to orchestrate pro-inflammatory responses mediated via the innate and adaptive immune system. The finding that the (*R*)-DOI-evoked response was blocked by relevant concentrations of the selective 5-HT_{2A} receptor antagonist, volinanserin, but not by 5-HT_{2B} and 5-HT_{2C} receptor antagonists, provides strong evidence the 5-HT_{2A} receptor evokes the anti-inflammatory responses. Further evidence for a 5-HT_2 receptor involvement comes from the involvement of (multiple) **PKC** isoforms in the response; these are integral to the canonical signalling associated with the 5-HT_{2A} receptor.

The relatively very high potency of (*R*)-DOI (i.e. anti-inflammatory evoked responses at pM concentrations) was extraordinary, yet other psychedelic 5-HT_{2A} receptor agonists assessed in the same study, like LSD, displayed activity at concentrations more comparable to function in other in vitro assay systems (Yu et al., 2008). That other 5-HT_{2A} receptor agonists do not display this extra potency above their 'normal' pharmacology indicates that (*R*)-DOI may engage the 5-HT_{2A} receptor with a more favourable interaction to evoke the intracellular signalling relevant to the anti-inflammatory action. This is an area worthy of further study as it may offer fundamental information to help identify potential novel anti-inflammatory therapeutics based on the action of psychedelic drugs.

The Nichol's group have translated and extended their in vitro studies by demonstrating anti-inflammatory activity of psychedelic drugs in animal models in vivo. Thus, in one study, for example, systemic administration of (*R*)-DOI caused a dose-dependent inhibition of a TNFα-induced acute moderate inflammatory response in mice discernible from reduced circulating levels of IL-6 and a range of pro-inflammatory mediators in the aortic arch and small intestine (Nau et al., 2013). The 5-HT_{2A} receptor was implicated in mediating the (*R*)-DOI-evoked response because prior application of the 5-HT_{2A} receptor antagonist, volinanserin, prevented the anti-inflammatory actions.

The anti-inflammatory action of (*R*)-DOI upon the vascular tissue (and small intestine) is well reported; however, the effects on other peripheral tissues (e.g. colon, kidney, liver and adipose tissue) and the brain, where inflammation was also apparent, were not impacted by the (*R*)-DOI administration (Nau et al., 2013). This apparent tissue selectivity is intriguing and did not appear to correlate with 5-HT_{2A} receptor expression levels (mRNA), although this was not evaluated at a cellular level. An understanding of the apparent differential tissue-dependent anti-inflammatory action of (*R*)-DOI may inform mechanistic insight to assist rational drug design of novel anti-inflammatory agents. Nevertheless, the impact of (*R*)-DOI upon the aortic arch supports the potential pharmacological treatment of atherosclerosis given the known inflammatory involvement of this vascular structure (Kong et al., 2022; Libby, 2021), which interestingly also acts as a predictor of other vascular events including brain infarction (Amarenco et al., 1996).

In addition to activity in an animal model of acute inflammation in vivo, further work by the Nichol's group has also demonstrated anti-inflammatory activity in animal models of the chronic disease, asthma. The human condition is characterised by airway hyper-responsiveness, inflammation of the lungs, along with hyperproduction of pulmonary mucus. In a mouse model of asthma resulting from chicken ovalbumin (OVA) challenges (Nau et al., 2015) that evokes a relevant IgE-mediated pathology, repeated (*R*)-DOI pre-treatment prior to each OVA challenge reduced the airway hyper-responsiveness following a subsequent methacholine challenge. Analysis of the lungs (histology and homogenates), as well as the contents from bronchoalveolar lavage (BAL), demonstrated that (*R*)-DOI reduced immune cell

[2]e.g. https://www.proteinatlas.org/ENSG00000102468-HTR2A/single+cell.

infiltration of the lungs, including eosinophils, along with reducing levels of pro-inflammatory biomarkers (e.g. IL-5, IL-6, IL-13, GM-CSF and the monocyte chemo-attractant protein, MCP-1). Interestingly, the raised total IgE levels (and OVA-specific IgE levels) apparent in the model were not altered by the (*R*)-DOI pre-treatment, suggesting the (*R*)-DOI pre-treatment did not prevent the immunoglobulin response associated with the pathology (Nau et al., 2015).

The above animal model of asthma was subsequently modified to present animals with pre-existing pathology (i.e. a model of established asthma; Flanagan et al., 2019) that better mimics patient presentation of the disease. Hence, it was significant that with this model, daily dosing of inhaled (*R*)-DOI reduced the pathological airway responsiveness (assessed by enhanced pause) in vivo. Furthermore, analysis of pulmonary tissues and fluids identified that the (*R*)-DOI treatment also reduced various other characteristic pathological features (mucus hyperproduction, airway fibrosis and peribronchial inflammation), as well as changes in biomarker measures of the pathology, such as expression of IL-9, IL-13, IL-15, IL-33, GM-CSF, mucin 5AC, MMP-9 and TGFβ; the latter two at least being relevant to promoting the associated pathological fibrosis, which may indicate an action upon fibroblasts.

Evidence is also available that psychedelic drugs such as DMT reduce neuroinflammation, such as that associated with post transient middle cerebral artery occlusion in a rat model in vivo (Nardai et al., 2020). This procedure is also associated with an ischaemic lesion in the brain and impaired motor function. DMT treatment reduced the size of the ischaemic lesion and limited the impairment in motor function as well as reducing the associated neuroinflammation evident by reduced TNFα, IL1β and IL-6 expression (mRNA) and increased IL10 expression (mRNA) in the brain. Interestingly, these changes were mimicked by the circulating levels of the cytokines in the serum. However, given DMT is also a ligand for σ receptors (as well as 5-HT_2 receptors), and the ability of the σ receptor antagonist, BD1063, to prevent DMT's protective impact upon the ischaemic lesion (the effect of BD1063 upon the neuroinflammatory biomarker measures was not reported in the paper) implicates the σ receptor mediating the response upon the lesion size in this study. It should be noted, however, that BD1063 also displays appreciable affinity for rat brain 5-HT_2 receptors, albeit some 50 times lower than for σ receptors (Matsumoto et al., 1995), which may complicate pharmacological interpretation of this data. More direct evidence for a role for the 5-HT_{2A} receptor modulating neuroinflammation comes from a further study using the middle cerebral artery occlusion model, where psilocybin reduced the levels of the microglial/macrophage activation marker, Iba-1 (Yu et al., 2024), as well as reducing the size of the lesion and improving motor deficits. Psilocybin has also been shown to reduce neuroinflammation in a mouse model (Zanikov et al., 2023, 2024). Evidence for psychedelics to reduce human neuroinflammation is also available from human cerebral organoids (Dakic et al., 2017) where the psychedelic tryptamine secreted by the Colorado river toad (*Incilius alvarius*), 5-MeO-DMT, suppressed NFAT and NF-kB signalling that would deliver an anti-inflammatory action (e.g. Liu et al., 2017; Müller & Rao, 2010) and also evoked changes predicting inhibition of processes associated with neurodegeneration and brain lesions (Dakic et al., 2017). Of relevance to these latter studies, psilocybin (and the active metabolite, **psilocin**) and MeO-DMT fail to display any relevant affinity for σ receptors (see Low et al., 2025).

While it is apparent that psychedelic drugs like (*R*)-DOI and certain trytamine derivatives display clear anti-inflammatory actions, it is intriguing that this is not the case for all psychedelic molecules, or where anti-inflammatory actions are evident, differences in efficacy are sometimes apparent. Indeed, it may be considered very encouraging for the therapeutic potential that some psychedelic drugs display anti-inflammatory action at doses *below* those thought to be relevant for a psychedelic effect (taken from either head twitch responses in animals or psychedelic experiences in humans). Such findings may suggest that the precise mechanisms underlying the anti-inflammatory effects are yet to be understood and may again indicate novel signal transduction associated with the anti-inflammatory action of 5-HT_{2A} receptor agonists.

A further potential benefit evident from the studies investigating the anti-inflammatory potential of psychedelic drugs is their tendency to not reduce inflammatory biomarkers below basal 'non-inflamed' levels (e.g. Nau et al., 2013), which mirrors results from in vitro studies (e.g. Yu et al., 2008). This suggests the pharmacological strategy may offer significant therapeutic advantages over, say, glucocorticoid steroid therapy that causes a general dampening of the immune response sometimes below normal functional levels that can be detrimental to the patient.

1.4 | Evidence for anti-inflammatory actions of psychedelic drugs from clinical trials

1.4.1 | Psilocybin

In a placebo-controlled trial with 60 healthy participants split 1:1 (drug:placebo), a single oral psychedelic dose of the pro-drug, psilocybin (0.17 mg kg^{-1}), which is metabolised to the pharmacologically more active drug psilocin, was assessed for impact upon inflammatory biomarkers. Psilocybin administration quickly reduced the plasma levels of the pro-inflammatory cytokine, TNFα (by around 20%, 1 to 2 h post-administration; Figure 1). At the same time points, some other classic pro-inflammatory cytokines (IL-1β, IL-6 and IL-8) and C-reactive protein (CRP) were not altered relative to the pre-drug baseline level (Mason et al., 2023). The relatively short half-life of TNFα in the blood (mins to hours; Calvano & Coyle, 2012) relative to, say, IL-6 (hours; Fong et al., 1990) or CRP (days; Noveck et al., 2014) would likely make lowering of circulating levels of the latter two unlikely over the relatively short time period of the trial. However, the plasma levels of IL-6 and CRP were lowered 7 days after the single dose of psilocybin (Figure 1), suggesting long-term anti-inflammatory effects after just a single dose—an action that perhaps mirrors the relatively long-term clinical effect to reduce, for example, symptoms of depression after acute drug administration (Carhart-Harris et al., 2016; Carhart-Harris et al., 2021; Davis et al., 2021; Goodwin

et al., 2022; Griffiths et al., 2016; von Rotz et al., 2022; for reviews see Vollenweider & Preller, 2020; McClure-Begley & Roth, 2022) and an ability to promote neuronal spine formation in the brains of animals (Grieco et al., 2022; Shao et al., 2021)—a so called neuroplastogenic response—which may underly some long-term symptom reversal following single or sub-chronic dose administration. The association between IL-6 and CRP is well known (e.g. Castell et al., 1989; Du Clos, 2000), with the latter also being an established biomarker for inflammation. A note of caution, however, is that the clinical trial reporting the anti-inflammatory action of the 'single dose' psilocybin used 'healthy donors' that had a history of drug abuse, including psychedelic drug use, which may complicate interpretation of long-term effects attributed to a single dose of the psychedelic drug.

In apparent contrast, retrospective analysis of serum from three clinical trials assessing the impact of psilocybin reported *increases* in TNFα (and IL-8) levels at time points at least 1 week after the drug administration, and at 4 weeks or more, IFNα and IL-10 levels were increased (the latter considered primarily an anti-inflammatory cytokine). Caution is warranted, however, as the results presented at the 2023 American College of Rheumatology meeting (DiRenzo et al., 2024) arise from a mixture of participants (healthy individuals and patients with depression, anxiety or cancer), which also complicates interpretations.

There are also negative results from clinical trials, thus Burmester et al. (2023) failed to detect *significant* changes in serum levels of CRP and urokinase-type plasminogen activator (suPA; another biomarker of inflammation with the benefit of being less affected by circadian rhythms; Haupt et al., 2019; Thurison et al., 2015) and plasma levels of TNFα 23 h following a psychedelic dose (0.22 mg kg^{-1}) of psilocybin. However, it should be noted, and was also commented upon by the authors of the study, that there were non-significant reductions in levels of CRP (32% decrease) and TNFα (83% reduction). It was recognised that this open-label trial without placebo control was underpowered with the recruitment of only 16 healthy volunteers (13 of whom were psychedelic drug naïve) rather than the estimated 80 recruits required for sufficient power to detect significant responses.

1.4.2 | Other psychedelic drugs

In a trial involving healthy controls and also patients with treatment-resistant depression, a single administration of the psychedelic concoction, ayahuasca—a 'recreational brew' containing the pharmacologically active psychedelic compound, **N,N-dimethyltryptamine**—reduced plasma CRP levels in both groups (i.e. either healthy controls or the patients) compared to placebo 2 days after ingestion. Interestingly, a greater lowering of depressive symptoms in patients post-ayahuasca administration was evident in those with greater reductions in CRP levels (Galvão-Coelho et al., 2020), linking the apparent anti-depressant action to the anti-inflammatory biomarker response. Serum IL-6 levels were also quantified at the same time points, but no clear changes were evident.

It is interesting to note that 5-HT_{2A} receptor-engaging psychedelic drugs (e.g. psilocybin converted in the body to the more pharmacologically active metabolite, psilocin, or N,N-dimethyltryptamine from ayahuasca) assessed in clinical trials may evoke a transient pulse of cortisol release (for example, evident at around 1–2 h post-drug administration; Dos Santos et al., 2011; Hasler et al., 2004; Uthaug et al., 2020) that may at least in part contribute to the inhibition of immune cells and reduction in the secretion of inflammatory mediators, including the lowering of circulating levels of TNFα and IL-6 (review Glaser & Kiecolt-Glaser, 2005; Uthaug et al., 2020). However, it should be noted that not all clinical trials, where investigated, report an increase in cortisol levels; for instance, a psychedelic experience evoking dose of psilocybin (0.2 mg kg^{-1}, but not more than 15 mg total dose) failed to evoke an increase in serum cortisol; samples being assessed regularly up to 300 min post-drug administration (Gouzoulis-Mayfrank et al., 1999), suggesting inappropriate sample collection time points do not explain this negative finding.

Clearly, clinical trials investigating the anti-inflammatory effects of psychedelic drugs in healthy volunteers (i.e. participants not having known pathological inflammation) might be considered a difficult cohort to demonstrate inhibition of inflammatory biomarkers that are already at relatively low 'normal' levels. Therefore, it is perhaps not surprising that there are reported differences in the actions of psychedelic drugs to alter levels of inflammatory biomarkers in healthy volunteers. Particularly when various studies demonstrate that psychedelic drugs reduce some inflammatory markers down to 'normal' levels rather than a general immune suppression as is apparent generally with glucocorticoid steroid therapies. Future studies may be more informative—and perhaps generate more consistent responses—if the healthy volunteers receive an inflammatory challenge with, for instance, LPS (endotoxin) or individuals recruited with already raised inflammatory biomarkers—including patients with inflammatory disease. However, a clear challenge of clinical assessment of psychedelic drugs is a placebo effect—with the evident 'psychedelic action' of the drug signposting to the participant/patient the active agent in a 'placebo-controlled' study. While placebo effects are perhaps more troublesome in the interpretation of subjective outcomes from patients with psychiatric disease, an inhibitory impact of placebo upon inflammatory biomarkers with disease has been documented (e.g. Vollert et al., 2020). Furthermore, the use of a lower—but still psychedelic—dose of the drug may not be a suitable alternative to a 'placebo' given some evidence of anti-inflammatory actions occurring at relatively low concentrations of drug. Although, of course, if sub-psychedelic doses are effective in reducing inflammation—as has been suggested for some psychedelic drugs—then this circumvents the issue. Clearly, results from well-controlled trials assessing the impact of psychedelic drugs upon pathological inflammation in patients are awaited eagerly to further assess the therapeutic potential of this pharmacological strategy. Of interest and potential relevance, a case report documents a patient with rheumatoid arthritis being relieved of his chronic symptoms by self-medicating periodically with psilocybin-containing mushrooms (Lin, 2020). While, of course, lacking a relevant control as well as issues around individual self-reporting, such anecdotal reports further encourage the testing of psychedelic drugs for the clinical benefit of patients with inflammatory disease.

2 | 5-HT$_{2A}$ RECEPTOR PHARMACOLOGY AND CELLULAR FUNCTION OF PSYCHEDELIC DRUGS

The primary target for psychedelic drugs included in the present review, the 5-HT$_{2A}$ receptor, is associated with multiple transduction pathways (Barclay et al., 2011; Berg et al., 1998; Flanagen & Nichols, 2018; Göőz et al., 2006; Greene et al., 2000; Kurrasch-Orbaugh, Parrish, et al., 2003; Kurrasch-Orbaugh, Watts, et al., 2003; Leysen et al., 1984; Low et al., 2025; Roth, 2011; Roth et al., 1986; Schmid & Bohn, 2010; Szabo, 2015; Xia et al., 2003). The G_q and β-arrestin pathways are best studied. Thus, in brief, the G_q pathway activates phospholipase C to promote hydrolysis of phosphatidylinositol-4,-5-biphosphate (**PIP$_2$**) to **IP$_3$** (inositol triphosphate) and DAG (diacylglycerol) with IP_3 increasing intracellular Ca^{2+} levels via engagement of the **IP$_3$ receptor** within the endoplasmic reticulum and hydrophobic DAG recruits Ca^{2+}-dependent protein kinase C to the intracellular side of the cell membrane along with activation of this enzyme. The β-arrestin signalling system is independent of G-proteins and, as well as promoting engagement of the endocytotic machinery to remove the receptor from the membrane, also triggers downstream signalling via various kinases (e.g. Jean-Charles et al., 2017).

The phenomenon of biased agonism has been forwarded to explain potentially psychedelic versus non-psychedelic 5-HT$_{2A}$ receptor agonists. Using the surrogate of the mouse head twitch response (HTR) to predict psychedelic response potential (for review see Hanks & Gonzáles-Maeso, 2012), a series of 5-HT$_{2A}$ receptor agonists biased towards β-arrestin signalling were inactive (Wallach et al., 2023), yet their ability to inhibit the HTR evoked by DOI indicates that pharmacokinetic and brain penetration issues did not account for their lack of activity. Likewise β-arrestin-2 KO did not inhibit the HTR evoked by DOI (Schmid et al., 2008), although for the less receptor selective psychedelic drug, LSD, β-arrestin-2 KO, but not β-arrestin-1 KO reduced by around two-thirds the LSD-evoked HTR. As there was a near complete block of the LSD-evoked HTR by the 5-HT$_{2A}$ receptor antagonist volinanserin (Rodriguiz et al., 2021), this suggests other signalling pathways may come into play. In contrast, 5-HT$_{2A}$ receptor agonists biased towards G_q signalling evoked the HTR, suggesting psychedelic activity. Furthermore, in this study, the efficacy in the HTR model correlated with the 5-HT$_{2A}$ receptor G_q-efficacy but not 5-HT$_{2A}$ receptor β-arrestin2-efficacy (Wallach et al., 2023). In addition, the ability of the $G_{q/11}$ inhibitor, YM-254890, as well as the phospholipase C (PLC) inhibitor, edelfosine, to essentially fully inhibit DOI-evoked HTR further forwards involvement of the 5-HT$_{2A}$ receptor G_q-PLC pathway mediating the HTR with further support from an earlier study using $G_{\alpha q}$ KO mice, where the DOI response was attenuated (Garcia et al., 2007). In this latter study, the lack of complete inhibition may be explained by other G proteins being involved such as G_{11} (Wallach et al., 2023).

It would appear that a threshold level of intrinsic activity to activate the 5-HT$_{2A}$ receptor is required for agonists to evoke psychedelic responses, for instance, above 70% intrinsic activity in some studies (e.g. Ippolito et al., 2025; Wallach et al., 2023). As noted earlier, this depends on the measure of 5-HT$_{2A}$ receptor function complicating such criteria. Even so, this would not appear to account fully for expression of psychedelic activity. In addition, certain 5-HT$_{2A}$ receptor agonists, informed from the molecular action of psychedelic drugs but designed to minimise potential psychedelic activity, retain activity in animal models of psychiatric disease. As discussed in the succeeding texts, evidence is growing that the anti-inflammatory action of 5-HT$_{2A}$ receptor agonists displays a novel pharmacology.

2.1 | Novel pharmacology of anti-inflammatory action associated with psychedelic drugs

In terms of extending the understanding of the mechanism of action of psychedelic drugs and drugs informed from psychedelic drugs, an elegant study by the Nichol's group evaluated the in vitro and in vivo pharmacology of two structurally similar molecules, (*R*)-DOI and (*R*)-DOTFM Flanagan et al., 2024; Figure 2). Both drugs displayed similar potency and efficacy to activate the human recombinant 5-HT$_{2A}$ receptor using the canonical cell signalling readouts of G_q-mediated transduction leading to an increase in $[Ca^{2+}]_i$ and β-arrestin recruitment, that is, across these two transduction systems, the two drugs do not display a bias. Likewise, both drugs displayed similar potency and efficacy in the mouse HTR, indicating similar in vivo activity between the molecules, and it would be predicted that, like the known psychedelic action of (*R*)-DOI, (*R*)-DOTFM would act similarly to evoke a psychedelic response. Against this background pharmacology, the clear differential action between the two molecules in the mouse acute asthma model is remarkable. Thus, as also shown previously by the authors, a single dose of (*R*)-DOI (0.5 mg kg^{-1}) was essentially fully active to reverse methacholine-evoked airway hyperresponsiveness as well as the OVA-induced increases in expression (mRNA) of the pro-inflammatory cytokines, IL-6 and CXCL10. In contrast, the same dose of (*R*)-DOTFM was essentially inactive, with the approximately 20% lower molecular weight of (*R*)-DOTFM unlikely to be responsible for the difference here, emphasised by their near-identical potency in the in vivo HTR mouse model. The differential anti-inflammatory activity between these two otherwise pharmacologically similar molecules offers the exciting opportunity to investigate the biological mechanisms mediating the anti-inflammatory actions with potential non-canonical differential signalling mechanisms underlying the different anti-inflammatory activity. As first steps towards understanding the potential differential impact upon cell biology, Flanagan et al. (2024) used a proteomic strategy to identify differences in the proteins modulated by the two molecules. Intriguingly, numerous differences were identified. For instance, (*R*)-DOI, unlike (*R*)-DOTFM, reduced expression of proteins associated with the signalling of **Rho kinases** (**ROCKs**). This observation is particularly important given the considerable literature where reduced ROCK activity reduces airway hyper-responsiveness, lung fibrosis and inflammation (Bei et al., 2016; Chiba et al., 2010; Guan et al., 2013; Kume, 2008; Yang & Shi, 2021). Consequently, ROCK inhibition is recognised as a potential therapeutic pharmacological strategy. **Arginase 1** was another affected protein

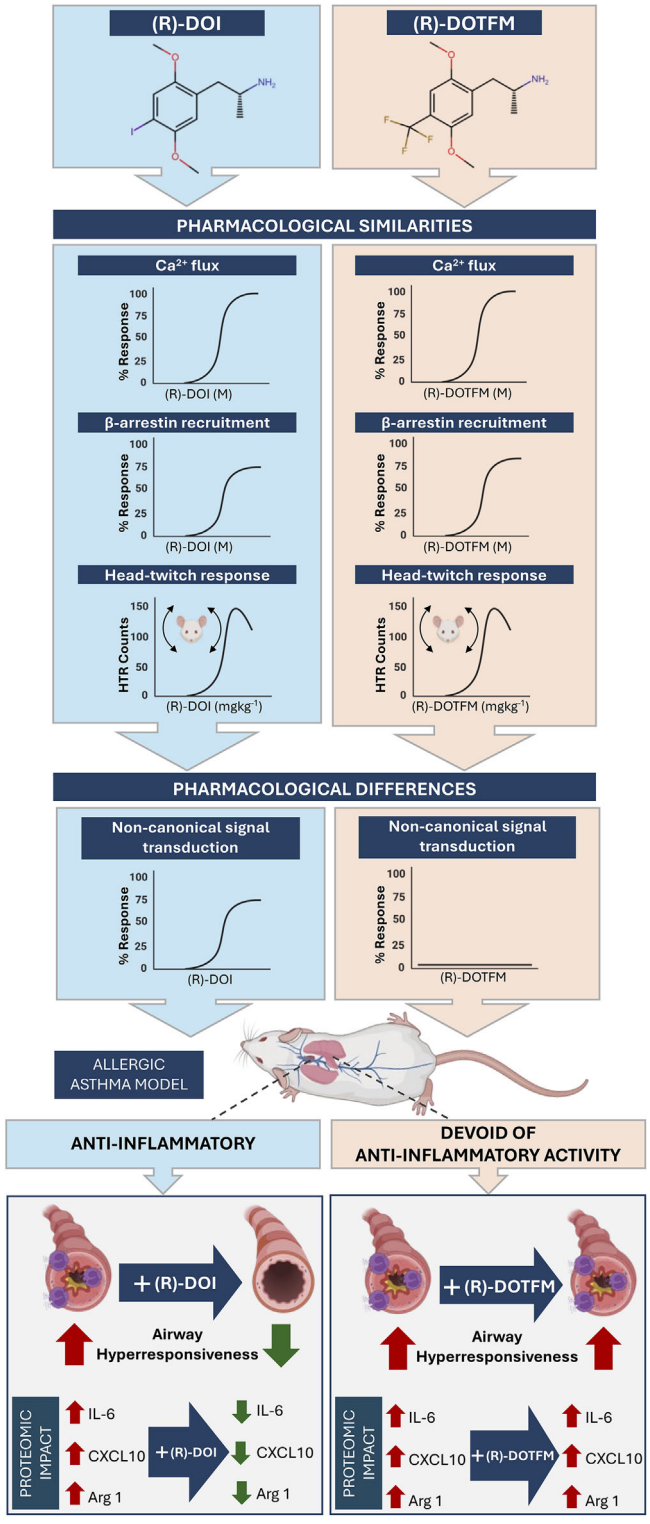

FIGURE 2 Differential anti-inflammatory actions of (*R*)-DOI and (*R*)-DOTFM in a mouse model of allergic asthma in vivo. Comparable pharmacology in vitro (5-HT_{2A} receptor-mediated second messengers; $[Ca^{2+}]_i$ and β-arrestin recruitment) and in vivo (mouse head twitch response [HTR] predicts clinical psychedelic activity). Data were redrawn or derived from Flanagan et al., 2024. Arg 1, Arginase 1.

of interest, displaying increased expression because of OVA treatment. This effect was reversed by the (*R*)-DOI treatment, but not by the (*R*)-DOTFM treatment (Flanagan et al., 2024; Figure 2). Thus, it would be predicted that (*R*)-DOI would reduce hydrolysis of endogenous L-arginine, thereby reducing L-ornithine and urea, leading to reduce inflammatory cell proliferation and collagen production, the latter by reducing proline availability to reduce fibrosis (Campbell et al., 2013; Flanagan et al., 2024; Wynn, 2004), although opposing actions upon inflammatory pathways are also apparent in some other studies (e.g. Monticelli et al., 2016; Shosha et al., 2023; West et al., 2023). Collectively, this elegant work from Charles Nichol's laboratory implies that 5-HT_{2A} receptor agonists that activate pathways in addition to the G_q/β-arrestin transduction pathways will form the basis of a novel therapeutic pharmacological strategy.

3 | DRUGS INFORMED BY PSYCHEDELICS BUT DEVOID OF PROBABLE PSYCHEDELIC ACTIVITY; POTENTIAL THERAPEUTIC ACTIVITY

It is well recognised that medicine-induced psychedelic activity is undesirable because of worries for patient safety that will rightly concern regulatory authorities. Hence, it is significant that some recent enticing developments in the field provide evidence that a therapeutic drug with pharmacology informed by psychedelic drugs but without psychedelic actions may be realistic. We propose to call such compounds PIPI drugs (Psychedelic drug Informed but Psychedelic experience Inactive). Such PIPI drugs from a number of independent studies have now been reported (Cameron et al., 2021; Cao et al., 2022; Kaplan et al., 2022; Koenig et al., 2024; Lewis et al., 2023; Rasmussen et al., 2024). In the first study from David Olson's academic lab (Cameron et al., 2021), investigation of relevant pharmacophore-informed analogues of the psychedelic drug ibogaine (IBG) resulted in the identification of tabernanthalog (TBG), which displayed an interesting pharmacology. Like IBG, TBG was an agonist at the human 5-HT_{2A} receptor (G_q pathway mediated Ca^{2+} flux assay) with an intrinsic activity of 57% (compared to 82% for IBG), but unlike IBG, TBG was inactive in the mouse HTR, suggesting TBG would not evoke psychedelic experiences in humans. As discussed earlier, the lower intrinsic activity of TBG (i.e. less than 70%) is consistent with a lack of psychedelic potential, yet TBG still promoted neural plasticity responses in vitro and also displayed anti-depressant activity in mouse models in vivo, as well as reducing seeking behaviour of mice for drugs of abuse.

Similarly, the LSD analogue, Br-LSD (aka BOL-148), retained 5-HT_{2A} receptor activity—albeit at lower intrinsic activity than LSD (i.e. Br-LSD displayed 60% and 37% intrinsic activity at the 5-HT_{2A} receptor using G_q dissociation and β-arrestin recruitment readouts, respectively; Lewis et al., 2023). Predictably, Br-LSD did not evoke the HTR in mice yet retained neuroplastogenic activity in vitro and

anti-depressant activity in a mouse chronic stress behavioural model. Importantly, this anti-depressant action was reversed by the selective 5-HT_{2A} receptor antagonist, volinanserin. Fortuitously, there are both relatively recent and historical reports of Br-LSD being investigated in the clinic, which suggest a lack of psychedelic activity. However, the volunteers and patients were able to perceive the drug above a placebo response when asked the question 'Do you feel peculiar in any way?' (Bertino et al., 1959; Cerletti & Rothlin, 1955; Ginzel & Mayer-Gross, 1956; Isbell et al., 1959a, 1959b; Jarvik et al., 1955), or in an open label study, participants reported 'flabby' feelings or a 'light drunk' sensation (Karst et al., 2010). One clinical report, however, suggested mild LSD-like reactions in response to initial Br-LSD administration (Turner et al., 1959).

The Cao et al. study (2022) identified an extended region of the 5-HT_{2A} receptor in addition to the canonical orthosteric binding site that recognised certain psychedelic molecules in a particular pose. Furthermore, ligand engagement in this extended binding pocket influenced biased agonism that led to the structural model that informed synthesis of β-arrestin-biased agonists. Two such compounds, IHCH-2079 and IHCH 7086, that lacked predictive responses of psychedelic activity in the mouse HTR, displayed antidepressant activity in mouse behavioural models that was blocked by the selective 5-HT_{2A} receptor antagonist, volinanserin.

The Kaplan et al. study (2022) used a novel approach of screening an ultra-large virtual adapted library using a homology model derived from the 5-HT_{2B} receptor, which is structurally closely related to the 5-HT_{2A} receptor (Kaplan et al., 2022). Subsequent refinement with biological evaluation resulted in two molecules, (*R*)-69 and (*R*)-70, with 5-HT_{2A} receptor-biased agonism towards G_q relative to β-arrestin-2 signalling. Intrinsic activity (>70%) for the G_q signalling may suggest the molecules would possess psychedelic activity, yet in the mouse HTR model (*R*)-69 displayed limited activity (around 30% above vehicle relative to LSD), and (*R*)-70 was inactive relative to the vehicle response. Interestingly, both drugs were able to suppress the LSD-evoked HTR—suggesting relevant 5-HT_{2A} receptor engagement within the brain but evidently without appropriate activation of the relevant signal transduction pathway(s) to deliver a strong HTR. Furthermore, neither (*R*)-69 nor (*R*)-70 were active in the pre-pulse inhibition model, which is also known to be sensitive to psychedelic agents. There was also inactivity in the open field locomotor activity test when either (*R*)-69 or (*R*)-70 were tested alone, although both molecules were able to reverse LSD-evoked locomotor activity, perhaps indicating the drugs might reduce the psychedelic response of LSD. However, and of considerable significance, both (*R*)-69 and (*R*)-70 retained anti-depressant and anxiolytic potential in established animal models. Given the reported interactions with LSD, this may be further evidence that the psychedelic and anti-depressant/anxiolytic responses arise from different mechanisms.

Delix Therapeutics, a company co-founded by David Olson, have reported in conference abstract form the development of PIPI drugs (e.g. DLX-001 and DLX-159) that display neuroplastogen effects and beneficial activity in animal models of depression without evoking a HTR in rodents (DLX-159; Rasmussen et al., 2024) suggesting a lack of psychedelic activity. Encouragingly another drug, DLX-001, investigated in Phase I studies with healthy volunteers in both single ascending dose (SAD) and multiple ascending dose (MAD) regimens failed to manifest 'psychotomimetic, hallucinatory or dissociative' symptoms at any of these doses investigated yet dose-dependent impact upon slow wave electroencephalogram (EEG) recordings were evident (Koenig et al., 2024), indicating CNS penetration of the drug confirmed by identified cerebrospinal fluid (CSF) drug levels. Independent peer review of the data packages is awaited.

Hence, there appears to be clear differential pharmacology of TBG, Br-LSD, IHCH-2079, IHCH 7086, (*R*)-69, (*R*)-70, DLX-001 and DLX-159 compared to typical psychedelic compounds (i.e. the listed compounds are predicted to not evoke psychedelic experiences), yet these compounds retain potential therapeutic activity in animal models of psychiatric disease. This highlights the potential advance towards a suitable safe therapeutic utilising this pharmacological strategy as a realistic goal. While yet to be reported, clearly the impact of these 'non-psychedelic' drugs in anti-inflammatory models would be revealing. Similarly, studying the impact of (*R*)-DOTFM (the psychedelic drug that lacks anti-inflammatory action in animal models) in depression models will help inform whether neuroplastic and anti-depressant activities of psychedelic and related PIPI drugs are distinguishable or not from anti-inflammatory activity. A commonality of action would help reveal underlying cell biological mechanisms and may broaden the indication potential of suitable drug candidates.

A further variation in the potential mechanism of action of psychedelic drugs—and perhaps PIPI drugs— comes from a series of experiments performed by David Olson's group, suggesting location bias has relevance to the psychedelic-relevant actions (Vargas et al., 2023). The concept arose from their finding that the lipophilicity of a series of tryptamine-based molecules correlated with their ability to evoke neuroplastogenic responses in vitro, which may underlie anti-depressant effects in vivo. The hypothesis was tested using a series of psychedelic molecules and their quaternary nitrogen derivatives (hence possessing a permanent positive charge) that retain comparable pharmacology but reduced lipophilicity to essentially thwart the crossing of cell membranes. These quaternary nitrogen derivatives did not display neuroplastogenic effects unless the neurones were electroporated to make their cell membranes leaky enough to allow cell entry. These neuroplastogenic effects were prevented by the 5-HT_{2A} receptor antagonist, ketanserin. However, in the absence of electroporation, a quaternary nitrogen derivative of ketanserin that retains 5-HT_{2A} receptor antagonist action did not block these effects. The study from the Olson lab if replicated would appear to have solved the dilemma that 5-HT itself does not display psychedelic activity. 5-HT is a relatively polar molecule and does not readily cross intact cell membranes without the expression of the 5-HT bidirectional transporter, **SERT**. Thus, delivery of 5-HT to the intracellular environment of neurones (via electroporation or heterologous expression of SERT) evoked neuroplastogenic effects and remarkably artificial expression of SERT by pyramidal neurones in the pre-frontal cortex allowed the HTR in mice following administration of the 5-HT releaser, *p*-chloroamphetamine (an action not evident in wild-type

mice). Previous indirect evidence in the literature also supports the ability of intracellular 5-HT to evoke a HTR because high doses of the cell membrane permeable precursor of 5-HT, **5-HTP**, can evoke the HTR. This response can be reduced, but not prevented, by a *N*-methyltransferase inhibitor (Schmid & Bohn, 2010), indicating N-methyltryptamines may be involved, although a component of the response may be mediated via intracellular 5-HT.

4 | SUMMARY AND CONCLUSIONS

A parsimonious summary of the data would be that the pharmacology of anti-inflammatory psychedelic drugs is still to be defined definitively. The range of models used, which differ in cell types, forms of activation and species, clearly complicate the generation of a consensus mechanism at present, yet perhaps indicate that the cell biology primarily responsible is not associated with canonical 5-HT_{2A} receptor signalling (i.e. G_q and β-arrestin pathways) and is yet to be defined. Clearly, an understanding of the cell signalling required for the anti-inflammatory action would help drug discovery projects by allowing relevant high-throughput assay technologies to facilitate drug discovery and development towards novel drug candidates. There is much research still to be performed, but this is encouraged by the potential therapeutic gains that may be achieved for conditions where clear substantial unmet clinical need remains, including inflammatory and psychiatric disorders. Indeed, depression and cardiometabolic co-morbidities may offer a unified target, given the established potential causal role of inflammation therein. In an ironic twist, the potential therapeutic activity of PIPI drugs gives a further nod to the positive consequences of medical research, which would have likely been unforeseen in the 1960s.

4.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/24 (Alexander, Christopoulos, Davenport, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, et al., 2023; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Amarosi, et al., 2023; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Annett, et al., 2023; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Beuve, et al., 2023; Alexander, Kelly, Mathie, Peters, Veale, Armstrong, Buneman, Faccenda, Harding, Spedding, Cidlowski, et al., 2023; Alexander, Mathie, Peters, Veale, Striessnig, Kelly, Armstrong, Faccenda, Harding, Davies, Aldrich, et al., 2023).

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CONFLICT OF INTEREST STATEMENT

NMB is a Director and shareholder in Celentyx Ltd. John Gordon is a Director and shareholder in Celentyx Ltd. Omar Qureshi and Cartherine Brady are shareholders in Celentyx Ltd. The other authors declare no relevant conflict of interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable as no new data were generated.

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