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PERSPECTIVE

Dimethyltryptamine (DMT): a biochemical Swiss Army knife in neuroinflammation and neuroprotection?

The inflammatory theory of many neuropsychiatric illnesses has become an emerging trend in modern medicine. Various immune mechanisms – mainly *via* the activity of microglia – may contribute to the etiology and symptomatology of diseases, such as schizophrenia, bipolar disorder, depression, or Alzheimer's disease (Deleidi et al., 2015; Khandaker et al., 2015). Unwanted and excess inflammation is most typically the result of dysregulated innate immune responses. Recognition of self-derived damage-associated molecular patterns (DAMPs) or pathogen-associated molecular pattern molecules (PAMPs) is usually leading to the activation of tissue resident immune cells including macrophages (microglia) and dendritic cells. They act as 'gatekeepers' continuously monitoring the tissue microenvironment for potential 'danger signals' by means of their pattern recognition receptors, such as Toll-like receptors or RIG-I-like receptors. Once a DAMP or PAMP has been recognized by a pattern recognition receptor various downstream signaling pathways are initiated, which eventually leads to the secretion of inflammatory cytokines and many other soluble factors important in the elimination of *e.g.* invading microbes. Pattern recognition receptors couple to nuclear factor kappaB (NF-κB), the master transcription regulator of inflammatory cytokines (*e.g.*, IL-1β, IL-6, TNFα) and chemokines (*e.g.*, IL-8/CXCL8) (Szabo and Rajnavolgyi, 2013). Macrophages and dendritic cells are also capable of antigen-presentation so they can initiate adaptive immune responses by priming naive T-cells. During inflammation of the central nervous system, polarization towards the T helper 1 and 17 (Th1, Th17) subsets is especially important as these T cells play a major role in the development of chronic inflammation and brain tissue damage in infectious diseases and autoimmunity (Kothur et al., 2016).

It has been known for decades that immunomodulation through serotonin/5-hydroxytryptamine receptors (5-HTRs) has the potential to regulate inflammation and prevent damage of the nervous tissue (Shajib and Khan, 2015). Recently another receptor has been added to the greater picture: the orphan receptor sigma-1 (Sig-1R). 5-HTRs and Sig-1R have been shown to be expressed ubiquitously in higher vertebrate tissues and mediate various processes, including the regulation of cognition and behavior, body temperature, as well as immune functions (Szabo, 2015). Both 5-HTRs and the Sig-1R use G protein-coupled (GPCR) pathways thereby modulating a plethora of cellular functions, such as cytokine/neurotransmitter release, proliferation, differentiation, and apoptosis. The molecular chaperone Sig-1R is located at the endoplasmic reticulum-mitochondrion interface and has an important role in the fine-tuning of cellular metabolism and energetics under stressful conditions (Hayashi, 2015). At the MAM, Sig-1Rs are involved in the regulation and mobilization of calcium from endoplasmic reticulum stores. Neuroprotection by Sig-1R activation can be attained by preventing elevations of intracellular calcium-mediated cell death signaling (Ruscher and Wieloch, 2015). Based on its central localization and function, pivotal physiological activities of the Sig-1R have been described such as indispensable role in neuronal differentiation, neuronal signaling, cellular survival in hypoxia, resistance against oxidative stress, and mitigating unfolded protein response (Pal et al., 2012).

Tryptaminergic trace amines (*e.g.*, N,N-dimethyltryptamine; DMT) as well as neurosteroids (*e.g.*, dehydroepiandrosterone) are endogenous ligands of the Sig-1R (Fontanilla et al., 2009). Tryptamines are naturally occurring monoamine alkaloids sharing a common biochemical – *tryptamine* – backbone. DMT was shown to be endogenously present in the human brain and in other tissues of the body, however the exact physiological role of this tryptamine has not been identified yet (Frecska et al., 2013). It has been shown that, besides its affinity for the Sig-1R, DMT also acts as an agonist at numerous serotonin receptors, such as 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} (Keiser et al., 2009; Ray, 2010). This wide-spectrum agonist activity may allow DMT to modulate several physiological processes and regulate inflammation through the Sig-1R and 5-HTRs. Indeed, DMT has been found to modulate immune responses through the Sig-1R under various conditions. These include the suppression of inflammation by blocking inflammatory cytokine and chemokine release of dendritic cells, as well as inhibiting the activation of Th1 and Th17 subsets (Szabo et al., 2014). The biochemical background of this extensive ability lies in the possible cross-talk of the GPCR-coupled downstream signaling of 5-HTRs/Sig-1R and other inflammatory pathways in immune cells, as well as the fine-tuning of cytokine feedback loops in peripheral tissues. Thus, in neuroinflammation, two major scenarios are possible: i) the modulation of cytokine production by brain resident microglia that implies a negative feedback regulation of inflammation *via* the induction of the release of anti-inflammatory IL-10 and TGFβ occurring subsequent of both 5-HTR and Sig-1R activation; ii) the direct/indirect control of NF-κB signaling and possibly other pathways (*e.g.*, MAPKs) involved in inflammation through intracellular kinases, adaptor proteins, etc (reviewed by Szabo, 2015). This way, the activation of 5-HTRs and Sig-1R may also interfere with the chemokine, inflammatory cytokine signaling of immune cells through intracellular mechanisms. Most of the receptors that are involved in psychedelic effects belong to the GPCR family or interact with GPCRs (Rogers, 2012). The role of 5-HTR/Sig-1R GPCR-coupled signals in the intracellular regulation and orchestration of NF-κB and MAPK pathways may be of particular importance regarding the complex neuroimmunological effects of DMT. Specific stimulation of the $5HTR_1$ and $5HTR_2$ receptor subtypes results in the activation of NF-κB and several MAPKs in many cell types including immune cells (Szabo, 2015). This coordinated cross-talk between MAPKs (including p38, MEKK1, ERK, and PI3K/Akt) and NF-κB leads to an intricate regulation of inflammatory responses

by the spatio-temporal adjustment of cytokine release. The inhibitory or stimulatory effect of GPCR activation on NF-κB and MAPK pathway kinetics is largely depending on the G-proteins that are involved. DMT, acting through mainly $5HTR_1$, $5HTR_2$, and Sig-1R receptors subtypes, regulates NF-κB and MAPKs *via* Gα (Gi and Gq families), and Gβγ proteins (Raymond et al., 2011). The Gq family of α subunits couple a large number of GPCRs to PLC-β, and many of these have been shown to activate NF-κB. This mechanism is based on the activity of the IκB kinases IKKα and IKKβ, as well as the PI3K pathway involving the serine/threonine protein kinase Akt (Xie et al., 2000). The PLC-β-IP3 axis-mediated release of calcium from intracellular stores results in the activation of the second messenger conventional protein kinase C (PKC). This calcium signal can also be attenuated by the activation of Sig-1R (Fontanilla et al., 2009), thus this receptor may couple to MAPK and NF-κB signaling and regulate inflammation (as well as apoptotic processes initiated by prolonged unfolded protein response) through this mechanism, as well. The above outlined picture suggests a direct control of NF-κB transcriptional regulation of chemokines, pro-inflammatory and anti-inflammatory cytokines, which may render DMT as a potentially useful therapeutic tool in a broad range of chronic inflammatory and autoimmune diseases, and pathological conditions connected to increased unfolded protein responseincluding but not restricted torheumatoid arthritis, multiple sclerosis, amyotrophic lateral sclerosis (ALS), Alzheimer's and Parkinson's disease, etc. However, the powerful hallucinogenic property of DMT poses an important problem that must be addressed in future drug design.

Protective and neuroregenerative effects of Sig-1R agonists have been reported in several *in vitro* and *in vivo* studies. The selective Sig-1R agonists 2-(4-morpholinethyl)1 phenylcyclohexanecarboxylate (PRE084) and cutamesine have been shown to strongly promote neuroprotective mechanisms and significantly increase neuronal cell survival and regeneration under various conditions, such as traumas, autoimmunity, and neurodegenerative disorders (Penas et al., 2011; Yamashita et al., 2015). Specific Sig-1R stimulation has also been found to greatly increase the levels of the glial cell-derived neurotrophic factor GDNF that promotes neuronal cell survival and differentiation (Penas et al., 2011). The neuroregenerative potential of DMT through the Sig-1R has been suggested earlier as multiple biochemical and physiological mechanisms exist, which facilitate the transportation and binding of DMT to the Sig-1R in the mammalian brain (Frecska et al., 2013). Thus DMT – as a natural, endogenous agonist at both the Sig-1R and 5-HTRs – is hypothesized to be an unique, many-faced pharmacological entity, which has many important roles in the immunoregulatory processes of peripheral and brain tissues, as well as involved in the promotion and induction of neuroregeneration in the mammalian nervous system.

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References

Deleidi M, Jäggle M, Rubino G (2015) Immuneaging, dysmetabolism, and inflammation in neurological diseases. Front Neurosci 9:172.
Fontanilla D, Johannessen M, Hajipour AR, Cozzi NV, Jackson MB, Ruoho AE (2009) The hallucinogen N,N-dimethyltryptamine (DMT) is an endogenous sigma-1 receptor regulator. Science 323:934-937.
Frecska E, Szabo A, Winkelman MJ, Luna LE, McKenna DJ (2013) A possibly sigma-1 receptor mediated role of dimethyltryptamine in tissue protection, regeneration, and immunity. J Neural Transm 120:1295-1303.
Hayashi T (2015) Conversion of psychological stress into cellular stress response: roles of the sigma-1 receptor in the process. Psychiatry Clin Neurosci 69:179-191.
Keiser MJ, Setola V, Irwin JJ, Laggner C, Abbas AI, Hufeisen SJ, Jensen NH, Kuijer MB, Matos RC, Tran TB, Whaley R, Glennon RA, Hert J, Thomas KL, Edwards DD, Shoichet BK, Roth BL (2009) Predicting new molecular targets for known drugs. Nature 462:175-181.
Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R, Jones PB (2015) Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. Lancet Psychiatry 2:258-270.
Kothur K, Wienholt L, Brilot F, Dale RC (2016) CSF cytokines/chemokines as biomarkers in neuroinflammatory CNS disorders: A systematic review. Cytokine 77:227-237.
Pal A, Fontanilla D, Gopalakrishnan A, Chae YK, Markley JL, Ruoho AE (2012) The sigma-1 receptor protects against cellular oxidative stress and activates antioxidant response elements. Eur J Pharmacol 682:12-20.
Penas C, Pascual-Font A, Mancuso R, Forés J, Casas C, Navarro X (2011) Sigma receptor agonist 2-(4-morpholinethyl)1 phenylcyclohexanecarboxylate (Pre084) increases GDNF and BiP expression and promotes neuroprotection after root avulsion injury. J Neurotrauma 28:831-840.
Ray TS (2010) Psychedelics and the human receptorome. PLoS One 5:e9019.
Raymond JR, Mukhin YV, GelascoA, Turner J, Collinsworth G, Gettys TW, Grewal JS, Garnovskaya MN (2001) Multiplicity of mechanisms of serotonin receptor signal transduction. Pharmacol Therapeut 92:179-212.
Rogers TJ (2012) The molecular basis for neuroimmune receptor signaling. J Neuroimmune Pharmacol 7:722-724.
Ruscher K, Wieloch T (2015) The involvement of the sigma-1 receptor in neurodegeneration and neurorestoration. J Pharmacol Sci 127:30-35.
Shajib MS, Khan WI (2015) The role of serotonin and its receptors in activation of immune responses and inflammation. Acta Physiol 213:561-574.
Szabo A (2015) Psychedelics and immunomodulation: novel approaches and therapeutic opportunities. Front Immunol 6:358.
Szabo A, Rajnavolgyi E (2013) Collaboration of Toll-like and RIG-I-like receptors in human dendritic cells: tRIGgering antiviral innate immune responses. Am J Clin Exp Immunol 2:195-207.
Szabo A, Kovacs A, Frecska E, Rajnavolgyi E (2014) Psychedelic N,N-dimethyltryptamine and 5-methoxy-N,N-dimethyltryptamine modulate innate and adaptive inflammatory responses through the sigma-1 receptor of human monocyte-derived dendritic cells. PLoS One 9:e106533.
Xie P, Browning DD, Hay N, Mackman N, Ye RD (2000) Activation of NF-kappa B by bradykinin through a Galpha(q)- and Gbeta gamma-dependent pathway that involves phosphoinositide 3-kinase and Akt. J Biol Chem 275:24907-24914.
Yamashita D, Sun GW, Cui Y, Mita S, Otsuki N, Kanzaki S, Nibu K, Ogawa K, Matsunaga T (2015) Neuroprotective effects of cutamesine, a ligand of the sigma-1 receptor chaperone, against noise-induced hearing loss. J Neurosci Res 93:788-795.