Commentary: Neurobiology and Therapeutic Potential of Cyclooxygenase-2 (COX-2) Inhibitors for Inflammation in Neuropsychiatric Disorders

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INTRODUCTION

Enzymes of the cyclooxygenase (COX) family catalyze the metabolism of arachidonic acids to prostanoids. In the central nervous system (CNS), COX-1 is constitutively expressed by neurons, astrocytes, and microglia; COX-2 is expressed by glutamatergic neurons in the cerebral cortex, hippocampus, and amygdala and is inducible in other cell types (1, 2). COX-2 and its products play important physiological role in synaptic plasticity and long-term potentiation but may also contribute to neuropathology by enhancing glutamate excitotoxicity, promoting neuronal cell death, and oxidizing endogenous cannabinoids (3, 4). Some studies suggest upregulation of COX-2 expression in inflammatory and neurodegenerative diseases as well as schizophrenia and bipolar disorder (1). Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit COX enzymes either selectively or non-selectively. In rat models, selective COX-2 inhibitors such as celecoxib inhibit microglial activation (5) and glutamate release (6) and enhance serotonergic and noradrenergic output in the prefrontal cortex (7, 8). Meta-analyses suggest possible benefit of adjunctive COX-2 inhibitors in the treatment of major depressive disorder (MDD) (9) and first-episode psychosis (10, 11); the general role of immunomodulation in these disorders has been recently reviewed (12).

Sethi and colleagues provide an important and timely review of pre-clinical and clinical studies investigating the use of COX-2 inhibitors across multiple psychiatric disorders including major depressive disorder, schizophrenia, bipolar affective disorder, autism spectrum disorder (ASD), and obsessive compulsive disorder (OCD). Other than a clinical trial protocol for celecoxib as an adjunct to vortioxetine in depression published in 2018 (13), their review of randomized controlled trials...
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The identification of immune-related bio-signatures will ideally assist in predicting risk of disease, prognosis, and response to therapy (14). Sethi et al. describe elevated pro-inflammatory markers as “consistently associated with neuropsychiatric symptoms.” While promising studies have begun to identify subpopulations of patients with MDD likely to respond to anti-inflammatory therapy (15), results of immune phenotyping in other disorders have been variable. A recent systematic review found that meta-analyses for MDD, ASD, bipolar disorder, and schizophrenia have consistently reported changes in only 16, 7, 8, and 7 individual inflammation-related factors in peripheral blood, respectively (16). The single meta-analysis of immune phenotyping studies in OCD was filtered out because of insufficient statistical power (16). Longitudinal data were lacking and state versus trait markers difficult to distinguish, markers were restricted to a few per study based on a biased candidate gene/cytokine approach, and the contribution of confounding factors—including childhood adversity, diet, and smoking—was potentially significant (16). Ultimately, longitudinal clinical characterization combined with a broad approach to immune phenotyping—as employed in a recent analysis of microarray data in MDD (17)—is likely a higher-yield approach both for biomarker discovery and for improving our understanding of how peripheral inflammation reflects or perpetuates psychiatric symptoms.

Sethi et al. also provide a common yet limiting perspective on microglial activation states. The disadvantages of the M1/M2 conceptualization of macrophage (18) and microglial (19) polarity in vivo have been previously discussed. As an in vitro construct that relies on stimulating cultured cells with a defined set of factors (20), its application to in vivo conditions is generally limited (21). Moreover, so-called M1 and M2 gene signatures often coexist in complex mixed phenotypes; the dichotomous paradigm is not supported by transcriptional profiling of human macrophages or monocytes activated by diverse ligands (22). Emerging evidence suggests that microglial subtype categorization should consider both their environment-dependent plasticity and subtypes with inherent functional specificity (23). Technologies that can assist in these efforts include two-photon imaging, whole-genome transcriptomic and epigenomic analyses at the cellular level, mass cytometry, and high-content experimental models (19).

DIVERSE NON-STEROIDAL ANTI-INFLAMMATORY DRUG MECHANISMS OF ACTION: THE SPECIFIC DRUG MATTERS

While all NSAIDS have anti-inflammatory, antipyretic, and analgesic properties attributable to prostaglandin inhibition, they vary with respect to COX selectivity (27) and likely with respect to COX-independent mechanisms (28–30). In the CNS, modulation of glutamate, serotonin, norepinephrine, and endocannabinoid signaling has been demonstrated for COX-2 inhibitors, while the role of non-selective NSAIDs in neurotransmitter function is less clear (3, 4, 6–8). NSAID use has also been associated with distinct gut microbial populations (31), an additional mechanism by which this class of drugs could affect neural development, cognition, and behaviour (32).

Few RCT’s have evaluated non-selective NSAIDs in primary psychiatric disorders, although the literature includes a negative RCT of naproxen in geriatric depression (33) and a study of adjunctive aspirin in schizophrenia suggesting some benefit (34). Clinical practice guidelines for the treatment of children with pediatric acute-onset neuropsychiatric syndrome (PANS) and pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) recommend the use of naproxen before celecoxib because of its “greater potency” (35), despite clinical studies showing benefit of adjunctive celecoxib in OCD (36, 37) and pre-clinical data demonstrating celecoxib-mediated enhancement of the serotonergic effects of fluoxetine in a rat model of anxiety (38). Moreover, observational studies have focused on NSAIDs as a class in children with PANS/PANDAS (39, 40). Given the significance of different COX isoforms and their
unknown relative “potencies” in the CNS, careful attention must be given to selection and evaluation of specific NSAIDs.

NEED FOR PEDIATRIC STUDIES AND EARLY INTERVENTION

A recent Danish population-based study suggested that environmental factors related to infection and inflammation are associated with the development of multiple mental disorders in children (41), adding to growing support for the link between immune activity and psychiatric symptoms early in life. However, there is currently little evidence to inform the use of adjunctive anti-inflammatory agents in children and adolescents with psychiatric disorders. Studies of peripheral inflammatory markers in this population have been equivocal, largely limited by similar methodological factors as adult studies (42, 43).

Early-life stress is more closely associated with overt inflammation prior to the development of neuropsychiatric symptoms. For example, childhood trauma is associated with significantly elevated peripheral levels of C-reactive protein, interleukin (IL)-6, tumor necrosis factor-α, and soluble urokinase plasminogen activator receptor (44, 45). Elevated IL-6 in childhood is in turn associated with increased risk of future depressive and psychotic symptoms in adolescence (46, 47). Stress-related epigenetic dysregulation in immune networks represents one mechanism by which childhood experiences may become biologically embedded (48), and a potential target for early intervention. Epigenetic modifications facilitate the phenotypic plasticity of macrophages, are critical to their role in maintenance of tissue homeostasis, and contribute to a form of innate immune “memory” that persists across the lifespan (49, 50).

Randomized controlled trials of COX-2 inhibitors as adjunctive therapies in children with treatment-resistant psychiatric disorders with a potential immune-mediated component may be warranted, beyond the single study of celecoxib in ASD noted by Sethi et al. Reassuring safety data exist for both celecoxib and non-selective NSAIDs, derived from studies of children with juvenile idiopathic arthritis (51) and familial adenomatous polyposis (52). This approach may be particularly relevant in OCD given that the majority of affected individuals experience disease onset in childhood or adolescence, with a persistence rate of approximately 40% (53). Clinical practice guidelines suggesting the use of celecoxib as a third-line agent in adults with OCD (54) and naproxen or celecoxib in children with PANS/PANDAS (35) provide a further clinical imperative for these studies.

CONCLUSION

Multiple lines of evidence suggest that aberrant inflammatory processes contribute to the pathogenesis of psychiatric disorders. Altered immune homeostasis may represent the consequence of
exposure to environmental factors including psychosocial stress together with cumulative genetic and epigenetic risk. Changes in neuroendocrine regulation, metabolism, gut microbiota, and health behaviours in turn affect peripheral and central immune cell phenotypes. For individuals with the most severe symptoms refractory to traditional treatments, modulation of the innate immune system with COX-2 inhibitors appears to be an attractive—though understudied—therapeutic approach.

In characterizing state and trait markers of disease and identifying appropriate patients for anti-inflammatory treatments, broad immunophenotyping is likely to be essential. Moreover, preclinical studies suggesting effects of COX-2 inhibition on neurotransmitter function would suggest that traditional markers of inflammation in the periphery may not be required for therapeutic effect. The implications of differences in COX selectivity as well as COX-independent effects of individual NSAIDs in the CNS require further study. Finally, stressful events in childhood drive peripheral inflammation and affect neurodevelopment. Given our increasing understanding of innate immune memory and its potential role in neurodevelopment and neurodegeneration, the likely bidirectional relationship between inflammation and psychiatric symptoms, and the known benefits of early intervention, treatment trials of COX-2 inhibitors in carefully-selected pediatric populations are warranted.

AUTHOR CONTRIBUTIONS

CW-R conceived of and drafted the article. SES provided critical feedback and reviewed the final version to be submitted.

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REFERENCES

1. Yagami T, Koma H, Yamamoto Y. Pathophysiological Roles of Cyclooxygenases and Prostaglandins in the Central Nervous System. Mol Neurobiol (2016) 53(7):4754–71. doi: 10.1007/s12035-015-9355-3
2. Kaufmann WE, Worley PF, Pegg J, Bremer M, Isakson P. COX-2, a synthetically induced enzyme, is expressed by excitatory neurons at postsynaptic sites in rat cerebral cortex. Proc Natl Acad Sci U S A (1996) 93 (6):2317–21. doi: 10.1073/pnas.93.6.2317
3. Yang H, Chen C. Cyclooxygenase in synaptic signaling. Curr Pharm Des (2008) 14(14):1443–51. doi: 10.2174/13816120878480144
4. Chen C, Magee JC, Bazan NG. Cyclooxygenase-2 regulates prostaglandin E2 signaling in hippocampal long-term synaptic plasticity. J Neurophysiol (2002) 87(6):2851–7. doi: 10.1152/jn.2002.87.6.2851
5. Kaizaki A, Tien LT, Pang Y, Cai Z, Tanaka S, Numazawa S, et al. Celecoxib reduces brain dopaminergic neuronal dysfunction, and improves sensorimotor behavioral performance in neonatal rats exposed to systemic lipopolysaccharide. J Neuroinflammation (2013) 10:45. doi: 10.1186/1742-2044-10-45
6. Lin T-Y, Lu C-W, Wang C-C, Huang SK, Wang S-J. Cyclooxygenase 2 inhibitor celecoxib inhibits glutamate release by attenuating the PGE2/EP2 pathway in rat cerebral cortex endings. J Pharmacol Exp Ther (2014) 351 (1):134–45. doi: 10.1124/jpet.114.2171372
7. Sandrini M, Vitale G, Pini LA. Effect of rofecoxib on nociception and the serotonin system in the rat brain. Inflammation Res (2002) 51(3):154–9. doi: 10.1007/PL00000287
8. Johansson D, Falk A, Marcus MM, Svensson TH. Celecoxib enhances the effect of reboxetine and glutoxate on cortical noradrenaline and serotonin output in the rat. Prog Neuropsychopharmacol Biol Psychiatry (2012) 39 (1):143–8. doi: 10.1016/j.pnpbp.2012.06.003
9. Faridhosseini F, Sadeghi R, Farid L, Pourgholami M. Celecoxib: a new anti-inflammatory treatment of depressive mood episodes. A systematic review and meta-analysis of randomized placebo-controlled trials. Hum Psychopharmacol (2014) 29(3):216–23. doi: 10.1002/hup.2401
10. Marinii S, De Berardis D, Vellante F, Santacroce R, Orsolini L, Valcher A, et al. Celecoxib Adjunctive Treatment to Antipsychotics in Schizophrenia: A Review of Randomized Clinical Add-On Trials. Mediators Inflammation (2016) 2016(1):3476240–8. doi: 10.1155/2016/3476240
11. Zheng W, Cai D-B, Yang X-H, Ungvari GS, Ng CH, Müller N, et al. Adjunctive celecoxib for schizophrenia: A meta-analysis of randomized, double-blind, placebo-controlled trials. J Psychiatric Res (2017) 92:139–46. doi: 10.1016/j.jpsychires.2017.04.004
12. Muller N. COX-2 Inhibitors, Aspirin, and Other Potential Anti-Inflammatory Treatments for Psychiatric Disorders. Front Psychiatry (2019) 10:375. doi: 10.3389/fpsyt.2019.00375
13. Fourrier C, Sampson E, Mills NT, Baune BT. Anti-inflammatory treatment of depression: study protocol for a randomised controlled trial of vortioxetine augmented with celecoxib or placebo. Trials (2018) 19(1):447. doi: 10.1186/s13063-018-2829-7
14. Leboyer M, Berk M, Yolken RH, Tamouza R, Kuperf D, Groc L. Immunomodulation: an agenda for clinical practice and innovative research. BMC Med (2016) 14(1):173. doi: 10.1186/s12196-016-0712-5
15. Chamberlain SR, Cavanagh J, de Boer P, Mondelli V, Jones DNG, Drevets WC, et al. Treatment-resistant depression and peripheral C-reactive protein. Br J Psychiatry (2012) 214(1):11–9. doi: 10.1192/bjp.2011.20166
16. Yuan N, Chen Y, Xia Y, Dai J, Liu C. Inflammation-related biomarkers in major psychiatric disorders: a disorder-arrest framework of reproducibility and specificity in 43 meta-analyses. Transl Psychiatry (2019) 9(1):233. doi: 10.1038/s41398-019-0570-y
17. Leday GGR, Vertes PE, Richardson S, Greene Jr, Regan T, Khan S, et al. Replicable and Coupled Changes in Inflammation and Cytokines and Specificity in 43 meta-analyses. Transl Psychiatry (2019) 9(1):233. doi: 10.1038/s41398-019-0570-y
18. Martinez FO, Gordon S. The M1 and M2 paradigm of macrophage activation: time for reassessment. Flinders Rep (2014) 6:13. doi: 10.12703/F6-13
19. Ransohoff RM. A polarizing question: do M1 and M2 microglia exist? Nat Neurosci (2016) 19(8):987–91. doi: 10.1038/nn.4338
20. Mills CD, Kincaid K, Alt JM, Heilman MJ, Hill AM. M-1/M-2 macrophages and the Th1/Th2 paradigm. J Immunol (2000) 164(12):6166. doi: 10.4049/jimmunol.164.12.6166
21. Orecchioni M, Ghoseh Y, Pramod AB, Ley K. Macrophage Polarization: Different Gene Signatures in M1(LPS+) vs. Classically and M2(LPS-) vs. Alternatively Activated Macrophages. Front Immunol (2019) 10:1084. doi: 10.3389/fimmu.2019.01084
22. Nahrendorf M, Swirski FK. Abandoning M1/M2 for a Network Model of Macrophage Function. Circ Res (2016) 119(3):414–7. doi: 10.1161/CIRCRESAHA.116.309194
23. Stratoudias V, Venero JL, Tremblay ME, Joseph B. Microglial subtypes: diversity within the microglial community. EMBO J (2019) 38(17):e101977. doi: 10.15252/embj.201910197
24. Holmes SE, Hinz R, Conen S, Gregory CJ, Matthews JC, Anton-Rodriguez JM, et al. Elevated Translocator Protein in Anterior Cingulate in Major Depression and a Role for Inflammation in Suicidal Thinking: A Positron
Emission Tomography Study. *Biol Psychiatry* (2018) 83(1):61–9. doi: 10.1016/j.biopsych.2017.08.005

25. Setiawan E, Wilson AA, Mizrahi R, Rusjan PM, Miller L, Rajkowski G, et al. Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. *JAMA Psychiatry* (2015) 72(3):268–75. doi: 10.1001/jamapsychiatry.2014.2427

26. Mondelli V, Vernon AC, Turkerhime F, Dazzan P, Pariente CM. Brain microglia in psychiatric disorders. *Lancet Psychiatry* (2017) 4(7):563–72. doi: 10.1016/S2215-0366(17)30101-3

27. Gan T, Diclofenac: an update on its mechanism of action and safety profile. *Curr Med Res Opin* (2010) 26(7):1715–31. doi: 10.1185/03007995.2010.486301

28. Ajmone-Cat MA, Bernardo A, Greco A, Minghetti L. Non-Steroidal Anti-Inflammatory Drugs and Brain Inflammation: Effects on Microglial Functions. *Pharmaceuticals (Basel)* (2010) 3(6):1949–65. doi: 10.3390/ph3061949

29. Diaz-Gonzalez F, Sánchez-Madrid F. NSAIDs: learning new tricks from old drugs. *Eur J Immunol* (2015) 45(3):679–86. doi: 10.1002/eji.201445222

30. Calvo-Rodriguez M, Nunez L, Villalobos C. Non-steroidal anti-inflammatory drugs (NSAIDs) and neuroprotection in the elderly: a view from the mitochondria. *Neural Regener Res* (2015) 10(9):1371–2. doi: 10.4103/1673-5374.165219

31. Rogers MAM, Vernon AC, Turkheimer F, Dazzan P, Pariante CM. The influence of non-steroidal anti-inflammatory drugs on the gut microbiome. *Clin Microbiol Infect* (2016) 22(2):178 e1–e9. doi: 10.1016/j.cmi.2015.10.003

32. Diaz Heijtz R. Fetal, neonatal, and infant microbiome: Perturbations and implications for the brain: a critical review. *Lancet Psychiatry* (2017) 4(10):793–8. doi: 10.1016/S2215-0366(17)30163-9

33. Fields C, Drye L, Vaidya V, Lyketsos C, Group AR. Celecoxib or naproxen as an adjuvant to fluvoxamine in moderate to severe obsessive-compulsive disorder: A double-blind, placebo-controlled, randomized trial. *Am J Geriatr Psychiatry* (2012) 20(6):505–13. doi: 10.1097/01.JGP.0b013e318227f4da

34. Laan W, Grobbee DE, Selten JP, Heijnen CJ, Kahn RS, Burger H. Adjuvant celecoxib potentiates the antianxiety and antidepressant effects of fluvoxamine. *J Clin Psychopharmacol* (2017) 37(2):145–52. doi: 10.1093/clinph/hox060

35. Kohler-Forsberg O, Petersen L, Gasse C, Mortensen PB, Dalsgaard S, Yolken RH, et al. A Nationwide Study in Denmark of the Association Between Treated Infections and the Subsequent Risk of Treated Mental Disorders in Children and Adolescents. *JAMA Psychiatry* (2019) 76(3):271–9. doi: 10.1001/jamapsychiatry.2018.3428

36. Milkowska P, Popko K, Demkow U, Wolańczyk T. Pro-Inflammatory Cytokines in Psychiatric Disorders in Children and Adolescents: A Review. *Adv Exp Med Biol* (2017) 1021:73–80. doi: 10.1007/5584_2017_24

37. Sayyah M, Boostani H, Pakseresht S, Malayeri A. A preliminary randomized controlled trial on the efficacy of ibuprofen and venlafaxine on anxiety and depression symptoms in children and adolescents. *J Pediatr Psychol* (2015) 21(5):642–9. doi: 10.1038/jnp.2015.67

38. Rasmussen LJH, Moffitt TE, Arseneault L, Danese A, Eugen-Olsen J, Fisher HL, et al. Association of Adverse Experiences and Exposure to Violence in Childhood and Adolescence With Inflammatory Burden in Young People. *JAMA Pediatr* (2020) 174(1):38–47. doi: 10.1001/jamapediatrics.2019.3875

39. Brown KD, Farmer GM, Spartz EJ, Farhadian B, Thienemann M, et al. Effect of Early and Prophylactic Nonsteroidal Anti-Inflammatory Drugs on Flare Duration in Pediatric Acute-Onset Neurosympathetic Syndrome: An Observational Study of Patients Followed by an Academic Community-Based Pediatric Acute-Onset Neuropsychiatric Syndrome Clinic. *J Child Adolesc Psychopharmacol* (2017) 27(7):651–9. doi: 10.1089/cap.2016.0193

40. Spartz EJ, Freeman GM, Brown K, Farhadian B, Thienemann M, Frankovich J. Course of Neuropsychiatric Symptoms After Introduction and Removal of Nonsteroidal Anti-Inflammatory Drugs: A Pediatric Observational Study. *J Child Adolesc Psychopharmacol* (2017) 27(7):652–9. doi: 10.1089/cap.2016.0179