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Can GPCR, such as Kappa Opioid Receptor, be a Viable Therapeutic Target for Reducing or Preventing Neuroinflammation?

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G protein-coupled receptors (GPCRs) are 7-transmembrane domain containing proteins that mediate a wide range of biological processes and are the most favored drug targets. Approximately 40% of modern drugs are designed to target specific GPCRs, directly as agonists or antagonists, or indirectly as modulators to intervene in the patho-physiological processes of diseases. For most neurological disorders where GPCR could contribute to disease progression, particularly those of chronic in nature, inflammation in the brain seems to be the culprit.

Opioids and their cognate receptors named Opioid Receptors (ORs) elicit the most potent analgesic effects and have been most widely exploited in medicine for centuries. Interestingly, specific endogenous OR ligands such as Dynorphin (Dyn), the endogenous ligand for the Kappa OR (KOR), are implicated in the pathogenesis of psychiatric disorders such as depression, drug addiction, and schizophrenia, etc. [1]. For these diseases, which all are chronic in nature, inflammation plays a critical role [2]. Recent studies of other chronic brain diseases, such as Parkinson's disease (PD) and HIV-infected dementia, also suggest a critical role for inflammation in disease initiation/progression. To this end, recent focus has been drawn to the biology of microglia, the major type of immune cells in the brain that mediate neuroinflammation. Importantly, Dyn and KOR are highly expressed in various brain regions including cortex, basal ganglia, hippocampus, amygdala, thalamus, midbrain, and brainstem. Further, in these brain regions, they are expressed not only in specific neuronal populations but also in microglia. Particularly relevant to PD, Dyn and KOR are highly enriched in Substantia Nigra (SN) and ventral tegmental area in the midbrain where Dopaminergic (DAergic) neurons are densely innervated and their loss signifies the progression of PD, which also correlates well with microglia accumulation. In rodent PD models, Dyn deficiency seems to exacerbate DAergic neuron loss, also suggesting that the Dyn/KOR system plays a role in neuroinflammation.

Feng et al. (2013) reported, for the first time, an intriguing mechanism by which the Dyn/KOR system protects Tyrosine Hydroxylase (TH^+) neurons, whose loss is a hallmark of the PD model, from LPS-induced neuronal death [3]. This study delineated the underlying molecular mechanism, that Dyn/KOR elevates and engages β-arrestin-2 (βArr-2) protein, which disrupts LPS-induced TLR4 signaling and actively sequesters TAB1 from TAK1 that could otherwise phosphorylates IKK/IκB to initiate nuclear translocation of p65 NF-κB, a master regulator of the synthesis of pro-inflammatory cytokines such as IL-1β, TNFα, and iNOS. Accordingly, they found that in microglia obtained from KOR depleted animals, βArr-2 fails to respond to Dyn, and that depleting KOR and/or blocking βArr-2 can significantly reduce the protective effects of Dyn in LPS-induced inflammatory shock in animals.

Supporting this mechanistic study, Yuferov et al. (2014) recently showed that, in postmortem brains of HIV-infected human subjects, *PDYN* (prodynorphin) and *OPRK1* mRNA levels are positively correlated with the anti-inflammatory marker CD163 but not with the pro-inflammatory marker CD68 in the anterior cingulate cortex, a terminal field in the mesocortical DAergic neuron system [4]. While it is difficult to discern the exact mechanism in postmortem studies, the authors speculated that increase in KOR mRNA might dampen the pro-inflammatory responses by recruiting CD163-presenting macrophages. This study indeed supports the notion and mechanism presented in Feng's study that the Dyn/KOR system could provide one physiological anti-inflammatory defense mechanism in the brain.

The results of Feng's study also shed light into new directions such as in exploiting βArr-2 as a general anti-inflammatory therapeutic target and in specifically targeting the OR system to reduce neuroinflammation.

First, KOR, when properly activated, can protect neurons by suppressing inflammation. This reinforces the decades old notion that the Dyn/KOR system communicates with dopamine neurons; but this appears to involve neuron-microglia interaction. The protective ability of Dyn/KOR is provided by, at least in part, its ability to suppress microglia toxicity in these cells.

Secondly, βArr-2, when activated by certain GPCRs, can elicit anti-inflammatory pathways in macrophages. Studies of βArr-2 have largely concluded the notion that it mediates desensitization and receptor down-regulation of GPCRs in neurons, which causes tolerance [5]. However, there has been a growing attention to alternative signal transduction pathways of βArr-2. For instance, βArr-2 depleted mice show vulnerability to inflammatory insults. The study presented by Feng et al. (2013) provides a proof-of-concept for the non-canonical activity of βArr-2 in anti-inflammation when certain ligand-GPCR pair like Dyn/KOR activates the βArr-2 cascade to disrupt the TAB1/TAK1 complex.

Thirdly, Dyn/KOR may also play a protective role in other neurodegenerative diseases and psychiatric disorders where inflammation can be a culprit, such as Alzheimer's disease, Huntington's disease, and multiple sclerosis, just to name a few. In fact, nonsteroidal anti-inflammatory drugs are used to reduce brain deterioration and improve cognition in Alzheimer's patients. Recently, psychiatric disorders have also been related to microglial abnormalities as shown in postmortem studies where microglial activation marked by IL-1β and brain infiltration of other immune cells is obvious in schizophrenia subjects. Whether Dyr/KOR is related to these neurodegenerative diseases and psychiatric disorders needs to be further examined.

Finally, an unsettled issue has to do with the kind of ligand-GPCR pairs that can engage βArr-2 in microglia. Not all the KOR agonists can elicit this pathway in microglia; obviously the coupling of the GPCR with its ligand is specific in terms of its ability to engage βArr-2 in microglia.

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In drug development, this may be the Holy Grail in the search of super anti-inflammatory molecules/compounds that can most specifically and effectively target the unique GPCR-βArr-2 pathway in microglia.

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