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Novel insights in phosphodiesterase 4 subtype inhibition to target neuroinflammation and stimulate remyelination

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In neurodegenerative and classically demyelinating disorders such as multiple sclerosis (MS), spinal cord injury (SCI), stroke, and Charcot-Marie-Tooth disease, glial functioning is compromised and nervous tissue integrity is lost. Recently, primary neurodegenerative disorders such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Parkinson's disease (PD) are increasingly linked to impaired oligodendroglia functioning upon neurodegeneration. Due to the destructive micro-environment created by nervous tissue damage, the progressive cellular loss in these disorders, and the amitotic nature of neurons, spontaneous endogenous repair process are limited in nature. Hence, there is a medical need for efficient therapeutic strategies capable of supporting neuro-reparative processes to occur, likely supported by improved oligodendroglia cell functioning.

The multifactorial pathogenesis of many neurodegenerative disorders comprises a bi-directional communication between the nervous system and the immune system. There is a growing body of evidence indicating that neurodegenerative and demyelinating disorders can be managed by either halting the destructive immunological interplay, stimulating repair processes, or both. Key in a variety of intracellular processes involved in both neuroregeneration and neuroinflammation is the second messengers 3′,5′-cyclic adenosine monophosphate (cAMP) (Knott et al., 2017). Intracellularly, cAMP is produced from ATP by adenylyl cyclase (soluble or membrane-bound), while being rapidly degraded by a class of enzymes called phophodiesterases (PDEs) (Sassone-Corsi, 2012). The superfamily of PDEs can be classified into eleven families (PDE1-11), which jointly cover twenty-one PDE genes or subtypes (e.g. PDE4A-4D). Each subtype can have multiple isoforms (e.g. PDE4D1-9), yielding a total of at least 77 different protein-coding isoforms (Paes et al., 2021). On the cellular level, the different contribution of PDE families, subtypes, and subsequently isoforms yields a unique cell type-specific 'PDE expression fingerprint'.

In the central nervous system (CNS) and immune cells, PDE4 is predominantly expressed among the different cAMP-specific PDE families (Li et al., 2018). In mammals, the PDE4 family comprises four genes, thereby encoding PDE4A, PDE4B, PDE4C, and PDE4D (Baillie et al., 2019; Paes et al., 2021). Among these different genes or subtypes, there is high degree of sequence similarity within the two regulatory domains (upstream conserved region (UCR) 1 and UCR2) and the enzyme's catalytic domain (Baillie et al., 2019; Paes et al., 2021). Due to multiple promotors and alternative splicing, PDE4 subtypes generate collectively 25 different mRNA transcripts encoding for PDE4 gene-dependent isoforms (Paes et al., 2021). The resulting isoforms can be categorized as long, short, and supershort depending on the presence of both UCR1 and UCR2, only UCR2 or a truncated UCR2 (Schepers et al., 2019).

Despite the widespread therapeutic potential of PDE4 inhibition in preclinical research, the development of PDE4 inhibitors for clinical use has been hindered by severe adverse effects such as diarrhea, nausea, and vomiting (Spina, 2008). As a result, only a limited amount of PDE4 inhibitors have been marketed because of their limited adverse effects and include roflumilast (Daliresp), crisaborole (Eucrisa), apremilast (Otezla), and ibudilast (MN-166), which are used to treat chronic obstructive pulmonary disease, moderate atopic dermatitis, psoriasis, and post-stroke complications respectively (Baillie et al., 2019). PDE4 inhibitors have previously been demonstrated to act immunomodulatory function, stimulate neuroregeneration, and enhance remyelination, rendering them valuable candidates for the treatment of multiple neurodegenerative disorders with either primary or secondary oligodendrocyte dysfunction (Schepers et al; 2019; Peng et al., 2020). Unfortunately, due to the high drug concentration required for sufficient CNS penetration, in combination with the widespread expression of PDE4, full PDE4 inhibitors coincide with even more and severe dose-limiting toxicities at their therapeutic dose in the CNS (McDonough et al., 2020).

New strategies should be implemented to rule out side effects while retaining the therapeutic potential of full PDE4 inhibitors. Interestingly, PDE4 subtypes and isoforms show distinct cellular distribution profiles, and specific PDE4 subtype inhibition has recently been demonstrated to orchestrate neuroinflammation and myelin regeneration, two key processes in MS pathogenesis (Schepers et al., 2023a). Whereas PDE4B subtype inhibition acts anti-inflammatory, PDE4D inhibition and more in particular PDE4D1/2 or PDE4D6 inhibition enhances remyelination (Schepers et al., 2023). The PDE4B inhibitor A33 and PDE4D inhibitor Gebr32a used in the abovementioned study did not show emetic side effects up to 300-fold the therapeutic dose (Schepers et al., 2023a). In addition, inhibition of the PDE4D isoforms that likely account for the emetic response in the neurons of the human area postrema has been uncovered and the remyelination promoting potential of PDE4D inhibition has been attributed to distinct isoforms. By avoiding affinity for PDE4D isoforms involved in the emetic processes, we propose that therapeutic applications that govern PDE4 subtype and isoform-specific inhibition to target neuroinflammation and stimulate remyelination highlight the potential future perspective of specific PDE4 subtype inhibition.

PDE4 subtype inhibition to treat demyelinating central and peripheral nervous system neuropathies: PDE4B and PDE4D have recently been described as novel therapeutic targets for managing distinct pathological processes of MS including neuroinflammation and myelin regeneration respectively. However, neuroinflammation and neurodegeneration are central processes involved in a wide range of disorders. Given the anti-inflammatory properties of PDE4B inhibition, and the myelin regenerative properties of PDE4D inhibition, it might be worthwhile to evaluate their clinical relevance in different demyelinating and neurodegenerative disorders.

***Demyelination-induced neurodegeneration*:** In demyelinating disorders, the myelin sheath surrounding the nerve fibers is damaged. By hampering nerve impulse conduction, neurological symptoms arise. In the CNS, oligodendrocytes are responsible for the production of myelin, while in the peripheral nervous system (PNS), this specialized cell type is called Schwann cells. Previous work has demonstrated that specific PDE4D inhibition stimulates remyelination in an animal model for the demyelinating CNS disorder MS (Schepers et al., 2023a). In line, PDE4D might be considered a potential treatment strategy for treating other demyelinating CNS disorders such as optic neuritis. Little is known about the therapeutic role of PDE inhibition in stimulating PNS repair and Schwann cell-mediated (re) myelination. In the PNS, cAMP regulation via PDE4 activity plays a crucial role in nerve repair. However, recently, it was demonstrated for the first time that PDE4 inhibition, by means of roflumilast, directly stimulates Schwann cell differentiation and subsequently remyelination in a 3D regeneration model (Schepers et al., 2023b). Based on the abovementioned findings of PDE inhibition on oligodendrocyte differentiation in the CNS, it, however, is worthwhile to further explore the therapeutic potential of PDE4 subtype inhibition on Schwann cell maturation and subsequently PNS myelination in peripheral nerve repair or peripheral neuropathies such as Charcot-Marie-Tooth disease.

***Insult-mediated coinciding demyelination and neurodegeneration*:** A CNS insult, such as a stroke or trauma leading to SCI or traumatic brain injury, evokes a complex interplay between neurodegenerative and inflammatory processes, which leads to prominent demyelination and neuroinflammation. Both SCI and stroke pathophysiology are characterized by a prominent

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neuroinflammatory response mediated by resident CNS microglia and infiltrated peripheral immune cells, which leads to both neuronal and glial cell death and therefore demyelination. The resulting chronic neuroinflammatory response subsequently impairs neuroregeneration. Given the anti-inflammatory properties of PDE4B inhibition, it might be worthwhile to evaluate the clinical relevance of inhibiting PDE4B to diminish the destructive neuroinflammation in the context of SCI or stroke to enhance functional recovery. Furthermore, recently, stimulating remyelination has been considered a valuable strategy for treating SCI and stroke. In SCI, the traumatic insult causes axons to be demyelinated, which subsequently impairs neural signaling and axonal functioning. Similarly in stroke, the interruption of blood flow to the brain can lead to oligodendrocyte death and therefore prominent demyelination. Promoting remyelination may therefore aid to restore axonal functioning and thereby neurological and functional outcomes.

***Pathology-induced neurodegeneration followed by impaired oligodendrocyte functioning and white matter damage*:** Recently, the importance of oligodendrocyte functioning has been highlighted in neurodegenerative pathologies such as Parkinson's disease, ALS, and Alzheimer's disease. The loss of myelin and white matter damage that results from oligodendrocyte dysfunction can have severe consequences for cognitive and motor function. In Parkinson's disease, white matter damage has been associated with cognitive impairment, while in ALS, oligodendrocyte dysfunction has been implicated in the disease's progression. In Alzheimer's disease, white matter damage can lead to memory impairment and cognitive decline. Therefore, understanding and restoring the role of oligodendrocytes, by for example inhibiting PDE4D, is critical for developing effective therapies to slow or halt disease progression of these pathology-induced neurodegenerative disorders.

Conclusion: The anti-inflammatory and remyelination promoting properties of PDE4B and PDE4D inhibition, respectively, hold promise for the treatment of MS and other neurodegenerative disorders. The choice of mono or dual therapy with PDE4B or PDE4D inhibitors highly depends on the specific disease pathogenesis, and careful consideration of the type and timing of PDE4 subtype inhibition is crucial. Furthermore, since the PDE4D isoform profile is characterized in area postrema neurons and oligodendroglia lineage, exploiting the cell type-specific PDE isoform expression fingerprint to alter cellular function fingerprint could offer an additional therapeutic strategy for improving functional recovery.

Perspectives: It became clear that the previously described neuroregenerative and anti-inflammatory properties of PDE4 inhibitors can be attributed to a PDE4D or PDE4B-dependent process respectively. These findings open new avenues for developing more targeted therapeutic strategies for treating different neurodegenerative and demyelinating disorders. The clinical translation of PDE4 inhibition has been impeded due to its emetic side effects, resulting in the shelving of numerous PDE4 inhibitors for further clinical development. However, the selective therapeutic benefits of PDE4 subtype inhibition suggest that it may be worthwhile to screen these shelved inhibitors for their selectivity against PDE4B and PDE4D isoforms. This could lead to the discovery of new compounds with therapeutic potential and favorable toxicological profiles that warrant their reevaluation. Furthermore, based on the literature, we know that multiple downstream effector proteins of cAMP signaling (e.g. protein kinase A (PKA) and exchange factor directly activated by cAMP (Epac)) are underlying the wide range of biological actions mediated by cAMP and therefore PDE signaling. Nevertheless, it remains poorly understood which exact downstream signaling pathway is activated upon PDE4B or PDE4D inhibition in glia cells or neurons, rendering a scientific knowledge gap. It has recently been demonstrated that independent cell signaling units on the nanodomain scale exist comprising different PDE4D isoforms, causing cAMP concentration gradients throughout the cell, which are altered differently upon upstream signaling cues. Unravelling the underlying nanodomain signaling unit can therefore hold the key for understanding the distinct biological actions resulting from PDE4D inhibition, thereby bridging the knowledge gap and identifying new downstream druggable targets. Taken together, the finding that PDE4 subtype specific inhibitors can safely diminish neuroinflammation or boost myelin regeneration opens a door for developing new, more specific, more potent and clinically relevant PDE4 subtype based inhibitors for potentially treating multiple neurodegenerative and demyelinating disorders.

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