Journal of Medicinal Chemistry

pubs.acs.org/jmc

Viewpoint

Beware the Receptor Variants

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Cite This: https://doi.org/10.1021/acs.jmedchem.3c02026

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ABSTRACT: The MAS-related genes (also known as MRGPRs) are a complex family of G protein-coupled receptors initially discovered in sensory neurons. Most of them are orphans, which means that they have no known validated endogenous ligands. Although MRGPRs bear great potential as drug targets, notably in itch and nociception, their study has been hampered by the scarcity or absence of potent and selective ligands, especially for the primate-specific MRGPRX subfamily.

Potent and selective ligands are powerful pharmacological tools to address the elusive function of a receptor. They pave the way to breakthroughs in receptor biology and drug discovery. In their *J. Med. Chem.* Featured Article, Marx et al. report on the discovery and development of such a tool for the understudied variant 83S of the orphan G protein-coupled receptor (GPCR) MRGPRX4.[1] GPCRs constitute the largest family of membrane receptors, with around 800 members distributed in several subfamilies (rhodopsin, adhesion, secretin, glutamate, frizzled). Their unparalleled versatility makes them the target of choice in drug discovery, as GPCRs play a pivotal role in a multitude of physiological processes. Important challenges remain to be solved to reveal the full therapeutic potential of many GPCRs. In particular, a vast number of these receptors are still described as orphans because they lack known endogenous ligands or are understudied due to a complex pharmacology. The group of MRGPRs is a large and hard-to-decipher family of at least 38 GPCRs in mammalian species that were named for their sequence homology with the oncogenic GPCR MAS1 (MAS-related genes, or MRGs).[2] They are dispatched into nine subfamilies: MRGPRA−MRGPRC and MRGPRH that are specific to rodents, MRGPRD−MRGPRG that are present in different mammalian species, including humans, and MRGPRX that is specific to primates.[3] Their expression was initially thought to be restricted to sensory neurons and their physiological function to be primarily linked to nociception.[2,4] However, the considerable efforts undertaken to characterize them revealed expression in several other tissues and a more diverse set of putative roles. Several MRGPRs are seen as promising drug targets in various indications such as analgesic, antipruritogenic (pruritus or itch being a sensation that drives a desire to scratch), and antihypertensive.[3] Although some ligands have been assigned to MRGPRs, they are still considered orphans, which impedes robust preclinical validation of their therapeutic potential. Furthermore, additional challenges exist with the subgroup of primate-specific MRGPRX, comprising four members, as they have no direct orthologs in rodents.[5] Therefore, the field needs particularly efficient, well-designed, and well-characterized pharmacological tools to crack these elusive and puzzling receptors.

Recently, it was reported by two independent teams that the poorly characterized MRGPRX4 receptor could respond to bile acids (notably deoxycholic acid, ursodeoxycholic acid, and taurodeoxycholic acid, see Figure 1) and was linked to cholestasis-induced itch.[6,7] Synthetic agonists such as Nateglinide, an antidiabetic drug associated with itch as a prominent side effect, were also found to activate the receptor.[8] A more potent derivative of Nateglinide, MS47134, has been recently developed and used to obtain the structure of MRGPRX4 in its active state.[9]

Interestingly, different natural variants of the human MRGPRX4 are known to exist.[10] For example, the position 83 has a leucine (MRGPRX4-83L) with a frequency of 3.4% in the human population, whereas the major variant (MRGPRX4-83S) has a serine in that position. Although the 83L variant has a lower prevalence, in most cases it is that variant that has been used to characterize ligands and obtain structural information on the receptor.[9] Marx et al. have now established an adapted set of tools consisting of cells lines expressing either variant and two relevant assays to measure arrestin recruitment and the $[Ca^{2+}]_i$ mobilization downstream of Gq, one of the natural transducer of MRGPRX4.[1] With these robust approaches, the authors answer key and timely questions regarding the pharmacology of the receptor and its variants. Their re-assessment of the established ligands reveals that the synthetic agonists identified so far display weak potencies or no activity on the major variant MRGPRX4-83S (Figure 1). With their unique tools in hand, they perform a novel screening and identify a hit compound that is further chemically optimized to produce a potent MRGPRX4-83S-selective agonist, PSB-22034 (Figure 1).

The molecules identified and the tools developed by the authors represent a notable achievement in the field of

Received: October 30, 2023

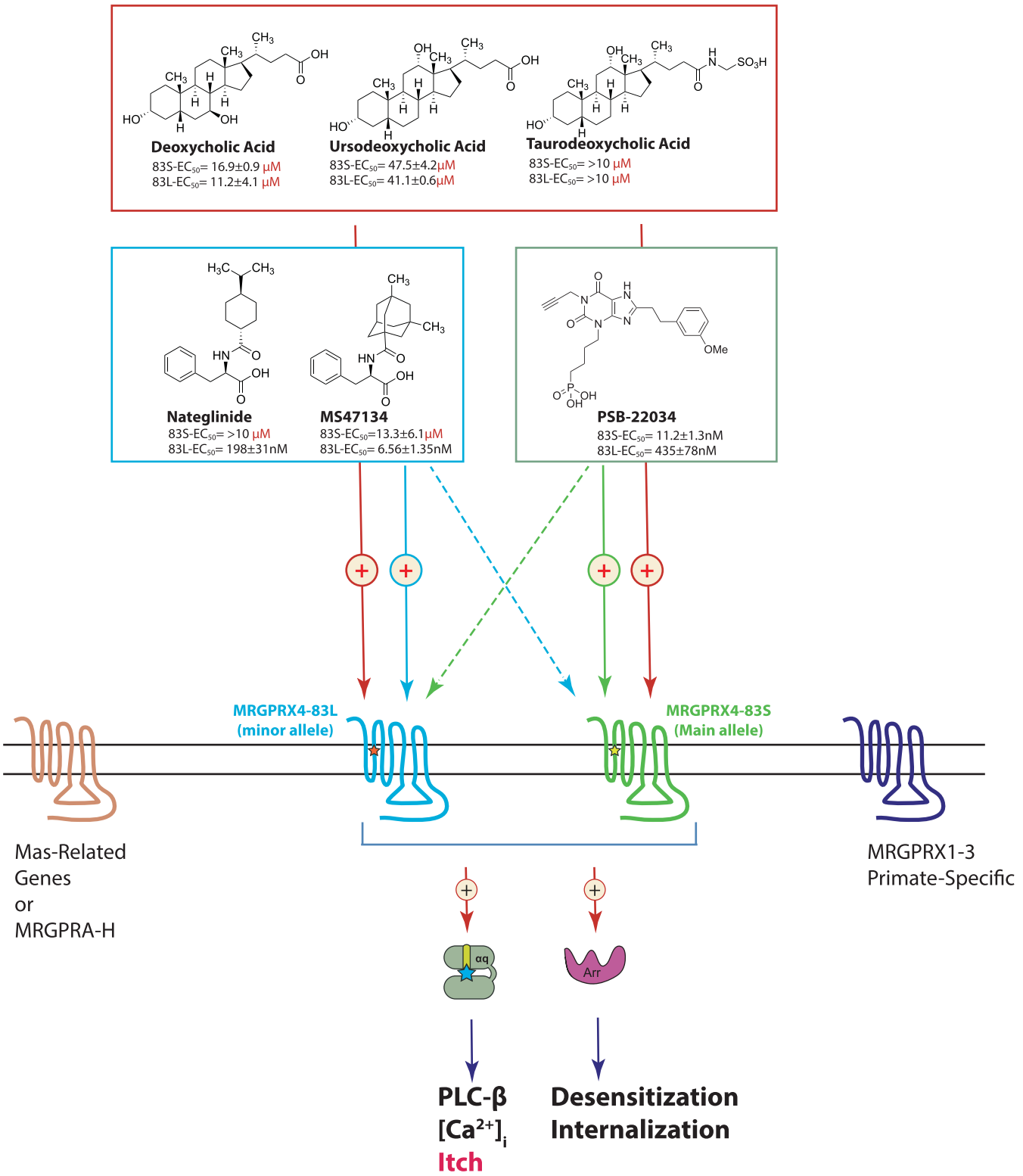

Figure 1. The primates-specific "MAS-related gene" MRGPRX4 receptor exists as two variants, 83S (major, 96.6% frequency) and 83L (minor, 3.4% frequency). Bile acid derivatives have been proposed as relevant endogenous agonists that convey cholestasis-induced itch and have balanced activity on both variants. Nateglinide and its derivatives (such as MS47134) are weakly or barely active at the major variant 83S. The study by Marx et al.[1] identified the first 83S-selective synthetic agonists, exemplified by PSB-22034. All EC_{50} values refer to an intracellular Calcium ($[Ca^{2+}]_i$) mobilization assay. See text and the related article for details.

MRGPR receptors. Significant advances in the validation of MRGPRX4 have been hampered by the limitations of models able to deliver information on its function in a relevant context as well as the lack of tools active on the most prevalent variant. The new ligand will unlock access to in vitro models based on human material. In these models, MRGPRX4 can be selectively invalidated by CRISPR/Cas9 and the contribution of the receptor measured in a specific way. The newly

https://doi.org/10.1021/acs.jmedchem.3c02026
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identified scaffold may also lead to antagonists active at the 83S variant that will permit advanced validation of MRGPRX4 as a drug target in cholestasis-induced itch. Furthermore, the new tool could pave the way to a refinement of the available receptor structures that would in turn enable the diversification of the existing repertoire of ligands. The published data on bile acid derivatives are compelling and robust, but the existence of several physiologically relevant variants with different pharmacology may necessitate improvement of the current models. It is tempting to speculate that currently unsuspected, more potent and pertinent, endogenous ligands may have been overlooked due to the use of 83L-centered models. In this context it would be interesting to investigate how itch manifests in people having the minor vs the major variant. Nateglinide-induced itch has been proposed to be the consequence of unwanted MRGPRX4 activation. Thus, given the low activity of Nateglinide on 83S, the proper assessment of the link between occurrence of this side effect and the presence of 83L variant should be established.

The Featured Article by Marx et al. goes beyond the topic of MRGPR receptors and is of broad interest for translational research. It highlights the significance of understanding receptor pharmacology in the context of human genetics. It was known already that naturally occurring mutations in receptors can affect their pharmacology and how they contribute to the pathophysiology of diseases. It is far less common to have synthetic compounds that are able to activate one variant with a significant selectivity ratio. In the near future, personalized therapeutic strategies could be envisaged, depending on the patient receptor variants in a particular disease. The fact that for MRGPRX4 such a compound already exists makes it a good candidate for such innovative therapeutic options. In conclusion, the discoveries reported by Marx et al. will unlock investigations on the function and drug target potential on MRGPRX4 and bring new conceptual highlights to the relevance of human GPCR variants for personalized medicine.

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https://doi.org/10.1021/acs.jmedchem.3c02026
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