0026-895X/10/7804-558–559$20.00
MOLECULAR PHARMACOLOGY

Mol Pharmacol 78:558–559, 2010

Vol. 78, No. 4
67645/3628835
Printed in U.S.A.

PERSPECTIVE

Mind Your Salts: When the Inactive Constituent Isn't

Richard R. Neubig

Department of Pharmacology and Center for Chemical Genomics, the University of Michigan Medical School, Ann Arbor, Michigan

Received July 22, 2010; accepted July 22, 2010

ABSTRACT

Many pharmacological agents include "inactive" constituents that are used to alter the solubility, stability, or pharmaceutical properties of a drug. These "salts" are often ignored, and the "active ingredient" gets all of the attention. Pamoic acid (4-[(3-carboxy-2-hydroxynaphthalen-1-yl)methyl]-3-hydroxynaphthalene-2-carboxylic acid) has been used in formulations of several drugs as pamoate salts. This *Perspective* highlights an *Accelerated Communication* in this issue (p. 560) that identifies pamoic acid as a potent activator of the orphan G protein-coupled receptor GPR35. This effect may contribute to the pharmacological actions of some agents that are prepared as pamoate salts. Thus, pharmacologists, regulators, and clinicians should "mind their salts" in considering differences among supposedly equivalent agents.

Introduction

In this issue of *Molecular Pharmacology*, Zhao et al. (2010) identify a novel pharmacological effect of the commonly used pharmaceutical salt pamoic acid to activate GPR35, an orphan G protein-coupled receptor (GPCR). A number of drugs (e.g., zaprinast, kynurenic acid, cromolyn sodium) from a range of pharmacologic categories can activate human GPR35 (Taniguchi et al., 2006; Wang et al., 2006; Yang et al., 2010) but most do so at concentrations higher than their therapeutic blood levels (Fig. 1). The activity of pamoic acid described in the present report is highly potent (IC_{50} ~100 nM), which raises important questions about the potential for this to play a role pharmacologically. The authors discovered the agonist effect of pamoic acid at GPR35 in a screen of known drugs for potential activators of GPR35 using the β-arrestin (β-Arr) recruitment method (Zhao et al., 2010), which is designed to identify functionally selective ligands that may differentially modulate different signal outputs. In this screen, they first turned up oxantel pamoate. Subsequent testing with the related compound pyrantel pamoate as well as its other salt form pyrantel tartrate and finally pamoic acid itself revealed that it was the pamoate moiety that carried the GPR35 agonist activity.

GPR35 is a $G_{i/o}$-linked GPCR that is expressed in intestine, immune cells, and dorsal root ganglion neurons (O'Dowd et al., 1998; Ohshiro et al., 2008) but its physiological functions are unknown. The recent demonstration that cromolyn disodium and nedocromil sodium activate GPR35 at nanomolar concentrations suggests a possible role in control of allergic reactions. Physiological studies in dorsal root ganglia also suggest a role in analgesia. Identification of new, pharmacologically tractable agonists would be desirable. The present study (Zhao et al., 2010) suggests a new option in this area. Furthermore, they have identified several potent antagonists of this very interesting orphan GPCR.

There are a number of clinically used compounds formulated as pamoate salts. In some cases, this is done to permit slow release from depot injections for antiparasitic treatments (pyrantel pamoate), antiandrogen therapy of prostate cancer (triptorelin pamoate), or improved compliance with antipsychotic therapies (olanzapine pamoate). In addition, the antihistamine compound hydroxyzine is formulated either as a pamoate salt (Vistaril) or as a hydrochloride salt (Atarax). They are often used for different purposes (sedation and antiallergy actions, respectively). Although this somewhat different clinical use may be due simply to marketing or prescribing habits, it is possible that the new information provided by Zhao et al. (2010) could indicate a mechanistic difference as well. Studies of pamoate blood levels after administration of the various pamoate salt compounds would help address this question.

Article, publication date, and citation information can be found at http://molpharm.aspetjournals.org.
doi:10.1124/mol.110.067645.
Please see the related article on page 560.

ABBREVIATIONS: GPCR, G protein-coupled receptor; β-Arr, β-arrestin.

Although this action of pamoate was identified in a β-Arr recruitment screen, the compound itself seems to produce good activation of the typical G protein output from GPR35. The extracellular signal-regulated kinase phosphorylation signal was completely blocked by pertussis toxin, which does not prevent β-Arr-mediated extracellular signal-regulated kinase signals. In addition, activation of rodent GPR35 by the phosphodiesterase inhibitor zaprinast leads to the pertussis-toxin sensitive inhibition of N-type Ca^{2+} channels in GPR35-expressing sympathetic neurons and inhibition of cAMP accumulation in nociceptive neurons in rat dorsal root ganglia. This G_i-mediated signaling may underlie the observed pamoate-mediated antinociception reported by Zhao et al. (2010). If so, this suggests an interesting new therapeutic approach.

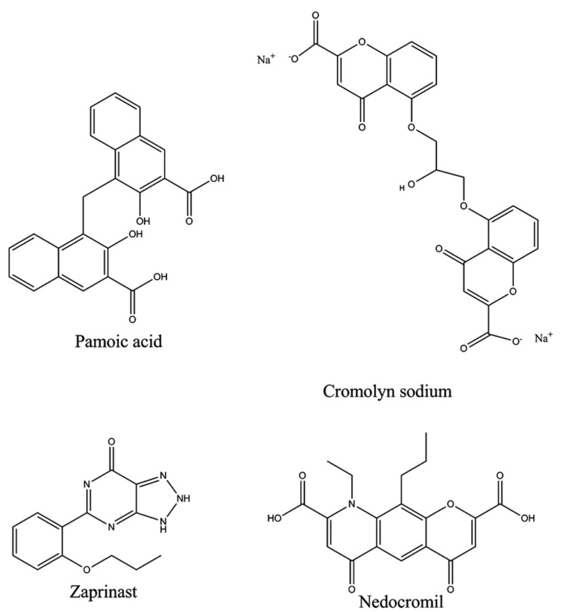

Fig. 1. Structures of several compounds shown to have agonist activity at GPR35.

There are several challenges to making use of these observations. Pamoate has two charged acidic groups that may limit oral absorption. In addition, pamoate has been reported to bind to other proteins including DNA polymerase β (Hu et al., 2004), suggesting the possibility of a relatively promiscuous protein interaction motif. Those other actions, though, are of relatively low affinity, which may not be a concern.

This study also points out a potential benefit from the numerous academic drug screening efforts currently under way. Unexpected observations such as the potent agonist activity of a common pharmaceutical salt may lead to both new understanding of existing drugs and to possible new drug development efforts. The rapid dissemination of such results from the academic sector, unimpeded by concerns about the impact on marketed compounds, can advance the understanding of drug actions.

References

Hu HY, Horton JK, Gryk MR, Prasad R, Naron JM, Sun DA, Hecht SM, Wilson SH, and Mullen GP (2004) Identification of small molecule synthetic inhibitors of DNA polymerase beta by NMR chemical shift mapping. *J Biol Chem* **279:**39736–39744.

O'Dowd BF, Nguyen T, Marchese A, Cheng R, Lynch KR, Heng HH, Kolakowski LF Jr, and George SR (1998) Discovery of three novel G-protein-coupled receptor genes. *Genomics* **47:**310–313.

Ohshiro H, Tonai-Kachi H, and Ichikawa K (2008) GPR35 is a functional receptor in rat dorsal root ganglion neurons. *Biochem Biophys Res Commun* **365:**344–348.

Taniguchi Y, Tonai-Kachi H, and Shinjo K (2006) Zaprinast, a well-known cyclic guanosine monophosphate-specific phosphodiesterase inhibitor, is an agonist for GPR35. *FEBS Lett* **580:**5003–5008.

Wang J, Simonavicius N, Wu X, Swaminath G, Reagan J, Tian H, and Ling L (2006) Kynurenic acid as a ligand for orphan G protein-coupled receptor GPR35. *J Biol Chem* **281:**22021–22028.

Yang Y, Lu JY, Wu X, Summer S, Whoriskey J, Saris C, and Reagan JD (2010) G-protein-coupled receptor 35 is a target of the asthma drugs cromolyn disodium and nedocromil sodium. *Pharmacology* **86:**1–5.

Zhao P, Sharir H, Kapur A, Cowan A, Geller EB, Adler MW, Seltzman HH, Reggio PH, Hynen-Genel S, Sauer M, et al. (2010) Targeting of the orphan receptor gpr35 by pamoic acid: a potent activator of ERK and β-arrestin2 with antinociceptive activity. *Mol Pharmacol* **78:**560–568.

Address correspondence to: Dr. Richard R. Neubig, Department of Pharmacology, 1301 MSRB III/1150 W. Medical Center Drive, University of Michigan Medical School, Ann Arbor, MI 48109-0632. E-mail: rneubig@umich.edu