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 (ODowd 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 (tiotroperlin 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.
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\textsuperscript{2+} channels in GPR35-expressing sympathetic neurons and inhibition of cAMP accumulation in nociceptive neurons in rat dorsal root ganglia. This G\textsubscript{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.

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

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