Does Vidarabine Mediate Cardioprotection via Inhibition of AC5?

Roland Seifert
Institute of Pharmacology, Hannover Medical School, Hannover, Germany
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ABSTRACT
There is an ongoing discussion about the value of adenylyl cyclase 5 (AC5) as drug target for treatment of heart failure. This letter discusses statistical, pharmacokinetic, and pharmacodynamic reasons why the recently proposed cardioprotective effects of vidarabine cannot be readily attributed to AC5 inhibition.

Membranous adenylyl cyclases (mACs) play a key role in signal transduction. ACs generate the second messenger cAMP following activation of G protein-coupled receptors and Gs-proteins. There are nine mAC isoforms (Sadana and Dessauer, 2009). On the basis of studies with AC5 knockout mice, it was proposed that inhibition of AC5 may constitute a pharmacological approach for treating heart failure and other age-related diseases (Vatner et al., 2013). Recently, Bravo et al. (2016) reported that the antiviral compound vidarabine exhibits cardioprotective effects in mice and pigs after reperfusion of previously occluded coronary arteries. The authors propose that the beneficial effects of vidarabine are mediated via AC5 inhibition, because in AC5 knockout mice vidarabine does not show an additional protective effect.

I have concerns about the authors’ interpretation for the following reasons:

1. In Fig. 3 the authors show that a cardio-specific AC5 knockout results in a modest decrease in infarct size. The addition of vidarabine results only in a statistically insignificant further decrease in infarct size. However, the data cannot be interpreted as evidence against involvement of mechanisms other than AC5 in drug action because the sample size was small (Spina, 2007; Mullane et al., 2015).

2. The authors applied vidarabine as short-term (5 minutes) infusion at a dose of 0.06 mg/kg, corresponding to a total dose of ~200 nmol/kg. Assuming equal distribution of the drug in the body (vidarabine is a very lipophilic drug), one can estimate that a steady-state concentration of around 200 nM is reached, but vidarabine plasma or tissue concentrations were not measured in the present study. This is an important point because vidarabine is not a potent AC5 inhibitor, i.e., vidarabine inhibits AC5 with IC50 values of ~2–10 μM, depending on the specific experimental setting (Brand et al., 2013; Seifert, 2014). Thus, the in vivo vidarabine concentrations are at best 10-fold lower than IC50 for AC5 inhibition, rendering AC5 inhibition minimal. In addition, this estimation does not even consider the fact that, in the study of Bravo et al. (2016), vidarabine was not continuously infused but only applied for a short time, so that drug concentrations were probably much lower than the estimated 200 nM. Moreover, vidarabine is a noncompetitive AC inhibitor, and inhibitor potency increases with increasing AC activity (Seifert et al., 2012). The IC50 values in the literature were obtained with strongly activated AC; i.e., with Gs stimulation and the diterpene forskolin (Braeunig et al., 2013; Brand et al., 2013). However, such a strong AC stimulation cannot be obtained in vivo, because there is no known endogenous forskolin analog (Seifert et al., 2012). Accordingly, one can assume that in vivo AC5 is much less sensitive to inhibition by vidarabine that the in vitro activated AC5.

3. Bravo et al. (2016) state that vidarabine is not a pure AC5 inhibitor. In fact, vidarabine is similarly potent at inhibiting AC5 and the closely related AC6 (Brand et al., 2013). This is a critical point because, like AC5, AC6 is expressed in the heart and is functionally relevant there (Gao and Hammond, 2011). Unfortunately, to this end, it has been impossible to develop an AC5 inhibitor with high selectivity relative to AC6 (Seifert et al., 2012; Brand et al., 2013). Thus, AC6 inhibition could contribute to the pharmacological effects of vidarabine under the conditions of the study of Bravo et al. (2016) provided that sufficiently high drug concentrations are reached.

In a recent commentary it was pointed out that toxicity of vidarabine is substantial, so that its FDA-approved clinical use is limited to topical applications (Seifert, 2014). Finally, considering AC5 knockout studies, it is probable that long-term therapy with an AC5 inhibitor passing the blood-brain barrier exhibits substantial neurotoxicity (Iwamoto et al., 2003).

ABBREVIATIONS: AC, adenylyl cyclase; mAC, membranous AC.
In summary, I have concerns about the authors’ conclusion that AC5 plays a major role in the effects of vidarabine in coronary reperfusion for statistical, pharmacokinetic, and pharmacodynamic reasons.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Seifert.

References


Address correspondence to: Dr. Roland Seifert, Hannover Medical School, Carl-Neuberg-Straße, Hannover, D-30625, Germany. E-mail: seifert.roland@mh-hannover.de