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Problems in the Pharmacological Applications of Organoselenium Compounds: Can they be Solved?

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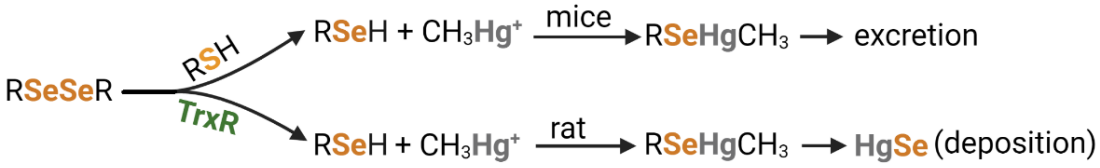
The role of selenium in life is very limited and the biological chemistry of selenium is mainly performed by the selenol (selenolate) group (-SeH) in a few selenoproteins.[1] Recently, a specific biosynthetic route for selenoneine or 2-selenyl-Nα,Nα,N α-trimethyl-L-histidine (3-(2-hydroseleno-1H-imidazol-5-yl)-2-(trimethyl-lammonio) propanoate)) has been identified,[2] indicating a potential role for a low molecular mass Se-containing molecule (LMMSe) in bacteria. The study of selenium in biology started nearly two hundred years ago when inorganic selenium forms were administered both in rodents and humans.[3a,b] Here, we will discuss the subfield of organoselenium compounds (OSeCs) chemistry, which we have called "pharmacological and therapeutic" potential applications of OSeCs.[3a] We will emphasize the potential metabolism of diphenyl diselenide [$(PhSe)_2$], ebselen (EbSe), and ebselen diselenide [$(EbSe)_2$] to their selenol intermediates (**Scheme 1**). We will present some indirect points of evidence that $(PhSe)_2$ and EbSe can act as "hidden selenol or LMM-SeH" intermediates and can interact with methylmercury (CH_3Hg^+) *in vivo* and *in vitro*.[3] $(PhSe)_2$ and EbSe can confer protection against CH_3Hg^+ toxicity *in vivo* and *in vitro*.[3b] The use of EbSe as a potential agent to lower the body burden of Hg in humans will be considered. Furthermore, given the recent findings about the synthesis of selenoneine in bacteria,[2] we can also speculate that the diselenide of selenoneine can be used as pharmacological agent to treat CH_3Hg^+ and acts also as hidden selenol in complex biological systems. The major drawbacks in the "pharmacological applications" of OSeCs will be discussed using $(PhSe)_2$, EbSe and $(EbSe)_2$ as generalizing examples that can be applied to the majority of OSeCs studied. The key problems in the advance of the potential pharmacological applications of OSeCs are: 1) the small number of studies determining the metabolism of LMMSe in relevant *in vitro* and *in vivo* models; 2) the frequent use of a single dose of LMMSe (particularly *in vivo* studies), 3) the low selectivity of their mode of action (quite different chemical structures have similar beneficial biological effects in an infinite array of *in vitro* and *in vivo* models of "diseases"), and 4) the non-specific interactions with thiol-containing proteins.[4] In short, the nearly phenomenological approaches (particularly *in vivo* studies), which are predominant in the pharmacological applications of OSeCs has to be changed to more rational approaches. The metabolism, reactivity and specificity of LMMSe with specific biological targets have to be tested *in silico* and in simple *in vitro* models before testing new LMMSe in living animals. This is important to adhere to EU directive about the use of vertebrate in scientific research (Directive 2010/63/EU, as amended Regulation (EU) 2019/1010). The development of new analytical methodologies to study the metabolism OSeCs are also highly needed to allow real advancements in the subfield of "pharmacological applications" of OSeCs.



Scheme1: Tentative metabolism of RSeSeR [$(PhSe_2$ or $(EbSe)_2$] to a selenol intermediate (either enzymatically via NADPH-Thioredoxin Reductase reduction -TrxR or by reducing thiol groups -RSH): complexation with CH_3Hg^+. In mice the excretion of the complex was increased, but in rats not (possibly deposition as mercury selenide, HgSe).

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