Pharmacological Chaperones

Subjects: Pathology

Contributor: Ludovica Liguori, Maria Monticelli, Mariateresa Allocca, Bruno Hay Mele, Jan Lukas, Maria Vittoria Cubellis, Giuseppina Andreotti

Pharmacological chaperones are small molecular weight drugs that are used when the primary cause of a disease is the instability of a particular protein. The hallmark of pharmacological chaperones is their ability to bind and stabilize their targets specifically. Pharmacological chaperones offer a hope to cure some genetic diseases with small drugs that can be administered orally and reach the central nervous system. This will not be possible for all the genotypes associated to a given diseases but requires a personalized approach.

Keywords: rare diseases ; drug repositioning ; protein stabilization ; lysosomal storage disorders

1. Introduction

Pharmacological chaperones are useful for curing diseases that are associated with protein mutants that are intrinsically active but unstable. This therapeutic approach has been proposed for several diseases, lysosomal storage disorders representing the most popular targets ([1] and references therein). Pharmacological chaperones are low molecular weight chemical molecules that bind and stabilize their target proteins [2]. Direct specific binding differentiates pharmacological chaperones from other low molecular weight chemical molecules, such as chemical chaperones and regulators of protein homeostasis, that promote correct processing of pathological mutants by different mechanisms.

2. Application

Pharmacological chaperones cannot be used by all patients affected by a given genetic disease. They are not useful in all the cases in which the protein is absent because the gene is affected by a deletion, a stop gain mutation, a splicing mutation, or a mutation occurring in the regulatory regions. Pharmacological chaperones are of no use if the active site is affected. Hence, some mutations can be excluded *ab initio*, the other ones, which are potentially responsive, must be tested individually. In some cases, the percentage of responsive missense mutations is high [3] in others is relatively low [4]. The situation is more complex in cases where patients are composite heterozygous and hetero-oligomeric proteins can be formed [5].

Most pharmacological chaperones have been discovered among reversible competitive inhibitors (or antagonists) and have been tested for their stabilizing effect. Competitive inhibitors often resemble chemically known substrates or products and an activity-based screening is straightforward. Indeed, competitive inhibitors are ligands that bind preferentially the folded state of an enzyme, and for this reason, they stabilize the protein. However, the stabilizing activity is required for chaperones, whereas the inhibitory activity is neither required nor desirable. Besides inhibitors, other ligands can act as pharmacological chaperones. It has been proposed to look for allosteric ligands that stabilize missense unstable mutants but do not bind the active site and do not inhibit the activity [6] [7]. Other types of small molecules, chemical chaperones and regulators of protein homeostasis, which act by different mechanisms, can potentiate the therapeutic effect of pharmacological chaperones acting in synergy [8] [9] [10].

In some cases, pharmacological chaperones to cure specific genetic diseases have been found among drugs approved for other conditions. Examples are provided by Ciclipirox, an antifungal medication that was proposed for the treatment of porphyria[7], by Pyrimethamine, which is a drug approved to treat toxoplasmosis and investigational for GM2-gangliosidosis [11], by Ambroxol and Bromhexine, both mucolytic agents, by Fluphenazine and Diltiazem, respectively an anti-psychotic and an antihypertensive drug, that were proposed for Gaucher disease [12] [13]. These findings suggest that drug repositioning can be very useful for the cure of rare diseases and should be considered to shorten the gap between bench and bedside [14].

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