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Therapies for galactosemia: a patent landscape

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Abstract

Galactosemia is the inherited inability to metabolise galactose. The most common results from a lack of galactose 1-phosphate uridylyltransferase (GALT) activity. The current treatment, removal of galactose from the diet, is inadequate and often fails to prevent long-term complications. Since 2015, three patents have been filed describing novel therapies. These are: (i) the use of aldose reductase inhibitors to reduce cataracts and, possibly other symptoms; (ii) salubrinal to stimulate cellular stress responses; (iii) mRNA therapy to increase cellular GALT activity. The viability of all three is supported by academic studies. The potential and drawbacks of all three are discussed and evaluated.

Keywords: GALT; galactose 1-phosphate uridylyltransferase; type I galactosemia; Leloir pathway; inherited metabolic disease; aldose reductase inhibitors; cataracts; salubrinal; PI3K/Akt signalling; mRNA therapy

Executive Summary

- Galactosemia is an inherited metabolic disease
- The most common form results from lack of GALT activity
- The current treatment is removal of galactose from the diet
- This is inadequate in many cases
- Three patents for novel therapies from 2015 to 2020
- Aldose reductase inhibitors may reduce the risk of cataracts
- They may also mitigate other symptoms, but this is currently uncertain
- Salubrinal may reduce oxidative stress by acting on PI3 kinase/Akt signalling
- Animal tests suggest this may alleviate brain and ovarian symptoms
- GALT encoding mRNA can be delivered to cells
- In animal models this results in expression of GALT in the liver
- Safe delivery across the blood-brain barrier would give the best outcomes
- Further work on galactokinase inhibitors is expected
- Gene editing may be used in the future to treat galactosemia

Introduction: Galactosemia

Galactosemia is the inherited inability to metabolise the hexose monosaccharide galactose [1]. The affected genes encode enzymes in the Leloir pathway of galactose metabolism [1, 2]. Four types are recognised, depending on the affected gene (Table 1). Of these, type I (galactose 1-phosphate uridylyltransferase deficiency) is the most common [3]. It is also, along with some cases of type III galactosemia, the type with the most severe symptoms. These include infant-onset cataracts, liver damage, cognitive impairment, movement disorders, susceptibility to bacterial infection and reduced fertility in females [4-7]. The only treatment is the removal of galactose (and its precursor, most importantly, lactose) from the diet [8]. This mitigates the symptoms, but it inadequate: most patients of type I galactosemia suffer lifelong physical and cognitive disability [7]. There is considerable interest in improved therapies which use novel agents, and the repurposing of drugs used in other diseases [9, 10]. However, none of these have been translated into clinical use. A search of global patents in the field of galactosemia from January 2015 to January 2020, returned three which cover novel therapies specifically for galactosemia. These are reviewed and evaluated below.

Aldose reductase inhibitors

Aldose reductase (aldehyde reductase; EC 1.1.1.21) catalyses the NADPH-dependent reduction of aldehydes, including aldose sugars such as glucose and galactose [11, 12]. This reaction is important in the formation of galactosemic cataracts [13, 14]. Galactose is reduced to galactitol (dulcitol) in the lens cells of the eyes. Unlike galactose, galactitol cannot be transported across the cell membrane. Its accumulation draws water into the lens cells by osmosis, resulting in apoptosis [15, 16]. Furthermore, galactose affects the expression of mRNA encoding aldose reductase in a tissue-dependent manner [17]. Aldose reductase inhibitors have been developed for the treatment of complications of diabetes [18]. Here, the enzyme catalyses the reduction of glucose to sorbitol which causes diabetic cataracts [19].

A 2019 patent, from Applied Therapeutics, covers the potential use of aldose reductase inhibitors in the treatment of galactosemia [20]. The scope is broad, essentially covering all inhibitors of this enzyme. Experimental evidence to support the claims in the patent rely on a homozygous GALT-null rat model. Two compounds (Figure 1) prevented the formation of cataracts in this rat model and reduced galactitol levels in the plasma, brain and liver without increasing galactose or galactose 1-phosphate levels. Further studies are planned to assess the longer-term effects of aldose reductase inhibitors on the cognitive and neurological symptoms of galactosemia in the rat model and human volunteers [20]. Academic studies reached similar conclusions: aldose reductase inhibitors result in lower galactitol levels and prevent cataracts in animal models of galactosemia [14, 21-23].

Cataracts are not considered to be the most serious symptom of galactosemia. In some cases, they resolve when the patient is placed on a galactose-free diet. Otherwise, surgery is required. However, cataract surgery is well-established and low risk. Thus, aldose reductase inhibitors are only likely to be of value if they also address cognitive and neurological symptoms. Little is known about the molecular causes of the nerve damage which leads to movement disorders in galactosemia. Excess galactose causes a two-fold increase in sodium concentrations in the endoneurial fluid in a rat model. This may draw water from the nerve cells, contributing to neuropathy [24]. This effect can be reversed by aldose reductase inhibitors suggesting that galactitol is responsible for this effect [25-27]. However, the effect is not seen in dogs and the role of

galactitol in human type I galactosemia pathology has been questioned [28, 29]. Cerebral atrophy has been observed in human patients, but there is no evidence for changes in the endoneurial fluid [30]. Magnetic resonance imaging has revealed the presence of millimolar levels of galactitol in the brains of galactosemic patients along with white matter abnormalities [31]. A blood-brain barrier permeable aldose reductase inhibitor would, presumably, reduce the amount of galactitol and any associated pathology.

There is also some evidence that aldose reductase inhibitors mitigate ovarian dysfunction in a rat model [32]. However, it is widely believed that galactose itself and galactose 1-phosphate also contribute to the pathology of galactosemia [33-35]. Aldose reductase inhibitors do nothing to reduce the levels of these metabolites and may even increase them – contrary to the claims of the patent [36].

Salubrinal to reverse defects in PI3K/Akt signalling

Salubrinal (Figure 2) is an experimental drug which inhibits eukaryotic translation initiation factor 2 subunit α (eIF2α) phosphatases and consequently up-regulates cellular stress responses [37]. A patent filed by the University of Utah covers the use of salubrinal and derivatives in the treatment of galactosemia [38]. Evidence supporting the claims in the patent showed that, in a GALT-null mouse model, salubrinal improved fertility compared with untreated controls. The PI3K/Akt signalling pathway is down-regulated in GALT-null mice; treatment with salubrinal reverses this. This reduced oxidative stress in brain and ovary. The drug had no detectable adverse effects on the mice, as assessed by birth weight and organ weights of treated animals [38]. The results are concordant with those reported in the academic literature by the same research group [39, 40].

The drug has yet to be tested in human patients. However, the animal data suggests it may be valuable in the preservation of fertility in female patients. Given that there is also evidence for reduced cellular stress in brain tissue, it may have additional beneficial benefits in all patients. Potentially these may include improved cognition or alleviation of movement disorders.

mRNA therapy

The ideal therapy for galactosemia would be to replace the affected enzyme. mRNA therapy attempts to do this by delivering mRNA to cells which is then translated to produce functional protein [41]. Costs are typically lower than delivering the protein itself [42]. A key issue is to overcome the chemical instability of mRNA, which might prevent its delivery to the sites of action. Typically, this is achieved by encapsulating the mRNA to protect it or chemical modification of the backbone to prevent chemical attack. Foreign single-stranded nucleic acids can also induce immune responses [43-45].

A patent filed by Modernatx Inc covers mRNA therapy for type I galactosemia using the human *GALT* sequence, as well as modified and optimised versions of this [46]. These modifications are proposed to increase the chemical stability and incorporate miRNA binding sites to reduce immune responses. It includes encapsulation methods with liposomes, nanoparticles and viruses. Evidence is presented that *GALT* mRNA partially rescued fibroblasts from a galactosemia patient when growing in galactose-enriched medium. In GALT-null mice, administration of the mRNA resulted in protein expression in blood and liver cells along with reduction in galactose 1-phosphate levels. Expression could be detected 14 days after administration. Biweekly administrated mRNA increased the

lifespan of GALT-null mice compared to untreated controls [46]. An academic study reported similar results. Human *GALT* mRNA encapsulated in liposomes and injected into GALT-null mice resulted in protein expression in the liver which persisted for two weeks. Repeated doses reduced galactose 1-phosphate levels in the liver, ovaries and brain. A single dose soon after birth reduced mortality of the pups fed on a milk diet [47].

In theory, this method represents the best hope of addressing the full range of galactosemia symptoms, since it replaces the dysfunctional protein. It remains to be seen if delivery systems can be developed which enable the mRNA to cross the blood-brain barrier. While some brain-related symptoms may be addressed by the removal of galactose 1-phosphate by circulation to the liver, others will require correction of aberrant glycosylation in neuronal cells [48]. This can only be achieved by restoring GALT activity in these cells. The longer-term effects of repeated doses of encapsulated nucleic acids also needs to be assessed.

Future perspectives

Other novel therapies are on the horizon for galactosemia. As yet, no patents have been filed describing pharmacological chaperones or enzyme replacement therapy for the treatment of galactosemia. Inhibition of GALK1 was proposed over two decades ago and several effective compounds have been described and some patents filed (but none in the last five years) [49-59]. Gene editing is rapidly becoming a realistic possibility in humans, albeit one fraught with ethical issues. Several patents describe novel methods for this and suggest galactosemia as a possible application, alongside many other genetic diseases, e.g. [60-77]. The current academic literature and patent landscape give significant hope that viable improved treatments for type I galactosemia will be available to patients in the next decade.

Conflicts of Interest Statement

The author has no conflicts of interest to declare.

Tables

Table 1: Types of galactosemia

Type	Affected gene	OMIN number[a]	Affected enzyme[b]	EC number	References
I	*GALT*	230400	Galactose 1-phosphate uridylyltransferase	2.7.7.10	[7, 78]
II	*GALK1*	230200	Galactokinase[c]	2.7.1.6	[49, 79]
III	*GALE*	230350	UDP-galactose 4'-epimerase	5.1.3.2	[80]
IV	*GALM*	na[d]	Galactose mutarotase	5.1.3.3	[81, 82]

Notes:

a. OMIN, Online Mendelian Inheritance in Man (https://omim.org/)

b. EC, Enzyme Commission (https://www.qmul.ac.uk/sbcs/iubmb/enzyme/)

c. A second galactokinase-like gene is known in humans – *GALK2*. The enzyme encoded, *N*-acetylgalactosamine kinase (EC 2.7.1.157), is not believed to function in the Leloir pathway.

d. Type IV is recently discovered and has not yet had an OMIN number assigned

Figure legends

Figure 1: Aldose reductase inhibitors tested in Patent WO 2019/023648 Al [20]. These are referred to as “compound A” and “compound B” in the patent. Systematic names were derived automatically using ChemDraw 19.0.0.2 (Perkin Elmer Infomatics, USA).

Figure 2: Compounds proposed to mitigate premature ovarian insufficiency [38]. (a) Salubrinol; (b) Generic structure covered by Patent WO 2018/232317 Al. R^1, R^2 and R^3 are variable groups; L is a variable linker.

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