Journal of Pharmacological Reports

OPEN ACCESS Freely available online

Mini-Review

# Towards an Advanced Understanding of the Pathogenesis of CNS Complications Associated with Galactosemia: Targeting Galactitol for Pharmacological Intervention with Govorestat, a Novel Aldose-Reductase Inhibitor

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## ABSTRACT

Galactosemia confers long-term Central Nervous System (CNS) complications and other difficulties in most affected individuals, despite newborn screening and dietary galactose restriction allowing survival into adulthood. These complications include speech, cognition, motor, and behavioral deficits, as well as cataracts and ovarian insufficiency in women. Endogenous synthesis of galactose far exceeds the level achieved through a galactose-restricted diet, limiting the long-term benefits of dietary control. Thus, an urgent medical need exists for those with this disorder. Although our understanding of Galactosemia has evolved over the last two decades, its pathophysiology has not been fully elucidated. Proposed causes of the complex symptomatology include newborn galactose exposure, non-adherence to the galactose-restricted diet, and Galactose-1-phosphate (Gal-1p) accumulation. However, none of these have been shown to account for the long-term complications of disease. Galactitol, an abnormal metabolite found in the blood of individuals with both Galactokinase (GALK) and Galactose-1-phosphate uridyltransferase (GALT) deficiencies, is a critical pathogenic cause of these complications. Galactitol is a toxic metabolite of galactose, produced by the enzyme aldose reductase only in the presence of excess galactose and is not found in healthy individuals. Several lines of evidence support the galactitol hypothesis of galactosemia-associated CNS complications, including animal models and clinical findings in individuals with galactosemia. Understanding the role of galactitol may provide a pathway to preserve CNS function in galactosemia.

**Keywords:** Galactokinase; Galactose; Neuropsychological; Pathogenesis; Galactosemia

## INTRODUCTION

### Galactosemia is a lifelong disease

Galactosemia is a multi-system disorder caused by a genetic inability to metabolize the sugar galactose [1]. Galactosemia is associated with acute life-threatening complications in the newborn period and chronic long-term complications that impact quality of life and day-to-day functioning [2-4]. While dietary restriction of galactose initiated during the early neonatal period usually prevents the severe acute features of galactosemia, a continued restricted diet fails to prevent neurological complications and premature ovarian insufficiency in women [5]. Endogenous synthesis of galactose by the body is higher than the amount of galactose consumed in food on a galactosemia diet [6-9]. There are currently no approved therapies to prevent the long-term complications of galactosemia. Govorestat is a novel, highly selective, brain penetrant aldose reductase inhibitor recently shown to lower galactitol level in patients with classic galactosemia [10].

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**Received:** 23-Jul-2024, Manuscript No. JPR-24-33138; **Editor assigned:** 26-Jul-2024, PreQC No. JPR-24-33138 (PQ); **Reviewed:** 12-Aug-2024, QC No. JPR-24-33138; **Revised:** 19-Aug-2024, Manuscript No. JPR-24-33138 (R); **Published:** 26-Aug-2024, DOI: 10.35248/JPR.24.08.220

**Citation:** Perfetti R, Waisbren SE, Mink JW, Bailey E, Shendelman S (2024) Towards an Advanced Understanding of the Pathogenesis of CNS Complications Associated with Galactosemia: Targeting Galactitol for Pharmacological Intervention with Govorestat, a Novel Aldose-Reductase Inhibitor. J Pharma Reports. 08: 220.

## LITERATURE REVIEW

### Neuropsychological complications

Long-term neuropsychological complications associated with galactosemia include developmental delays, speech and language delay and/or deficits, suboptimal intellectual functioning, gross and fine motor difficulties, behavioral abnormalities, and psychiatric disorders (depression and anxiety) [11-13]. Some case studies suggest progressive worsening of symptoms [14,15]. A recent cross-sectional analysis of 19 children with galactosemia explored the relationship between functioning and age, using age-appropriate standardized tests to assess neuropsychological domains of speech, cognition, motor skills and behavior [16]. All children were adherent to a strict galactosemia diet initiated at birth and had access to typical supportive services, including speech therapy, learning support and occupational therapy. Symptoms in younger children appeared to be less severe than symptoms in later childhood and adolescence in all domains. However, longitudinal studies are lacking to confirm the observation from the recent cross-sectional analysis [16].

The neuropsychological complications associated with galactosemia impact quality of life and day-to-day functioning, and create a substantial burden of care [17-19]. Speech deficits, speech production (verbal apraxia) and word-finding difficulties are the speech elements most often affected in individuals with galactosemia. These types of language deficits impair effective communication and comprehension [13,20-22]. Poor cognitive functioning also affects educational attainment and independent living [23,24]. Psychosocial and behavioral abnormalities, including psychiatric disorders and adaptive behavior, may result in isolation and dependence on a parent or caregiver throughout adulthood [17,18,23]. Motor skill deficiencies can impact performance in the early school years, including activities such as writing and drawing and may restrict opportunities for adult employment in physical occupations [4,13,25,26]. Thus, the impact of galactosemia extends beyond quality of life, with adults generally unemployed and relying heavily on caregivers or assisted living facilities [17,27].

### Pathogenesis of galactosemia

Exposure to galactose in the newborn period was thought to be responsible for early manifestations of galactosemia and that symptoms would resolve with removal of galactose from the diet [28]. However, many children who were never acutely exposed to galactose at birth (because of an older sibling with galactosemia or prenatal identification *via* genetic testing) experienced speech delay and cognitive deficits, suggesting that other factors, rather than exposure to galactose in the newborn period, are responsible for the long-term complications [29]. Non-adherence to the galactose-restricted diet was also proposed as the cause of learning deficits or other symptoms [30,31]. However, studies have demonstrated that endogenous galactose production exceedes the amount of galactose ingested in young children, casting doubt on this hypothesis [9,32-34].

Deficiency of Galactose-1-phosphate uridyltransferase (GALT) is the primary biochemical abnormality in classic galactosemia. The resulting accumulation of Gal-1p, which is the substrate for GALT, has been thought to impact protein glycosylation in multiple organs, including the brain. The hypothesis concerning abnormal glycosylation has been proposed as a contributing factor to the underlying CNS complications in this disorder. The elevation of Gal-1p has not been proven to be responsible for CNS damage. *In vitro* mechanistic studies with excess Gal-1p have failed to demonstrate a toxic effect, and protein glycosylation defects detected in older children and adults with classic galactosemia have not been shown to correlate with the long-term complications [35,36].

Galactonate is another compound involved in galactose metabolism and could, in principle, be considered in the pathology of galactosemia. Galactonate is formed *via* conversion of galactose by the enzyme galactose dehydrogenase. However, individuals with galactosemia have normal levels of galactose dehydrogenase and are able to convert galactose to galactonate efficiently. Although endogenous production of galactose may lead to increased flux of galactose to galactonate, galactonate itself is a non-reactive, nontoxic metabolite. Furthermore, it does not accumulate in blood and tissues because it can easily be metabolized or directly excreted in urine [37,38].

### Role of Galactitol in galactosemia

Recent evidence suggests galactitol may be the most important metabolite associated with complications in galactosemia. Galactitol is formed by conversion of galactose to a reduced sugar alcohol by the enzyme, aldose reductase-a reaction that only occurs at very high galactose concentrations and does not occur in healthy people [39-40]. Healthy people (without galactosemia) do not have measurable levels of galactitol in blood or tissues [41,42]. Galactitol (like other reduced sugar alcohols) is highly toxic and its accumulation intracellularly is associated with osmotic dysregulation, oxidative damage, and disturbances in redox potential in neurons [7,8,43,44].

A relevant evidence on the role of galactitol in causing neurological damage was derived from a study of patients with Galactokinase (GALK) deficiency. Unlike patients with GALT deficiency, GALK-deficient patients do not produce Gal-1p. However, they do have elevated levels of galactitol and many patients show neuropsychological deficits similar to those seen in GALT-deficient patients, pointing towards a role of galactitol, rather than Gal-1p, in the pathogenesis of galactosemia [36,45].

Animal models provide additional support to the role of galactitol in brain function. Deletion of GALK in GALT-null Drosophila reduced Gal-1p levels but did not prevent functional deficits [46]. GALT-null rats, which display elevated levels of galactose, galactitol and Gal-1p, display similar CNS complications as humans with Galactosemia, including learning, cognition and motor issues [47]. However, GALT-null mice, which display elevated galactose and Gal-1p levels but not elevated galactitol (because mice express very low levels of aldose reductase compared with rats and humans) do not display any CNS complications [48,49]. Treatment of the GALT-null rat model with an aldose reductase inhibitor decreased galactitol levels (without lowering elevated Gal-1p and galactose levels) and prevented CNS symptoms of disease (as well as cataracts) [50].

Elevated galactitol has been detected in the brains of children with classic galactosemia and it has been proposed that galactitol may be responsible for CNS complications such as pseudotumor cerebri reported in both patients with classic galactosemia and GALK deficiency [51-57].

Recent clinical data from a cross-sectional analysis of 47 children with classic galactosemia revealed a correlation between plasma galactitol levels and measures of speech/language, cognitive, motor and behavioral difficulties [58].

Thus, evidence is leading to a focus on galactitol and its role in complications associated with Galactosemia. Although galactitol levels are high in blood and tissues throughout the body in individuals with Galactosemia, damage and long-term complications are most pronounced in tissues with low cellular turnover, such as the brain and ovaries in females [13].

Govorestat is a novel, highly selective, brain penetrant aldose reductase inhibitor recently shown to lower galactitol level in patients with classic galactosemia [10].

## CONCLUSION

Galactosemia significantly affects CNS function, as well as emotional well-being and quality of life. Speech, cognition, motor skills and behavior are impaired in most individuals. Dietary restriction, while essential to prevent the acute symptoms of galactosemia, does not prevent long-term complications. Pharmacological inhibition of galactitol formation provides a compelling opportunity to prevent the troubling long-term consequences for patients.

## DECLARATION OF COMPETING INTEREST

RP, EB and SS are all employees and shareholders of Applied Therapeutics.

## AUTHOR CONTRIBUTIONS

SS and RP drafted the initial manuscript and critically reviewed and revised the draft manuscript. SW, JM, EB reviewed and revised the draft manuscript. All authors provided final approval of the draft for submission. All authors agree to be accountable for the accuracy and integrity of the work.

## FUNDING

This research did not receive any specific grant from funding agencies.

## REFERENCES

1. Demirbas D, Coelho AI, Rubio-Gozalbo ME, Berry GT. Hereditary galactosemia. Metabolism. 2018;83:188-196.
2. Pyhtila BM, Shaw KA, Neumann SE, Fridovich-Keil JL. Newborn screening for galactosemia in the United States: Looking back, looking around, and looking ahead. JIMD Rep. 2015;13:79-93.
3. Welling L, Bernstein LE, Berry GT, Burlina AB, Eyskens F, Gautschi M, et al. International clinical guideline for the management of classical galactosemia: Diagnosis, treatment, and follow-up. J Inherit Metab Dis. 2017; 40:171-176.
4. Hoffmann B, Dragano N, Schweitzer-Krantz S. Living situation, occupation and health-related quality of life in adult patients with classic galactosemia. J Inherit Metab Dis. 2012;35(6):1051-1058.
5. Frederick AB, Cutler DJ, Fridovich-Keil JL. Rigor of non-dairy galactose restriction in early childhood, measured by retrospective survey, does not associate with severity of five long-term outcomes quantified in 231 children and adults with classic galactosemia. J Inherit Metab Dis. 2017;40:813-821.
6. Schadewaldt P, Kamalanathan L, Hammen HW, Wendel U. Age dependence of endogenous galactose formation in Q188R homozygous galactosemic patients. Mol Genet Metab. 2004;81(1): 31-44.
7. Berry GT. The role of polyols in the pathophysiology of hypergalactosemia. Eur J Pediatr. 1995;154:S53-64.
8. Berry GT, Nissim I, Mazur AT, Segal SS. The rate of endogenous galactose synthesis in normals and patients with galactose-1-phosphate uridyltransferase deficiency 704. Pediatr Res. 1998;43(4):122.
9. Bernstein LE, van Calcar S. The diet for galactosemia. Nutrit Manag Inher Metab Dis. 2015:285-293.
10. Perfetti R, Bailey E, Wang S, Mills R, Mohanlal R, Shendelman S. Safety, pharmacokinetics, and pharmacodynamics of the new aldose reductase inhibitor govorestat (AT-007) after a single and multiple doses in participants in a phase 1/2 study. J Clin Pharmacol. 2024.
11. Waisbren SE, Potter NL, Gordon CM, Green RC, Greenstein P, Gubbels CS, et al. The adult galactosemic phenotype. J Inherit Metab Dis. 2012;35(2):279-286.
12. Potter NL, Nievergelt Y, Shriberg LD. Motor and speech disorders in classic galactosemia. JIMD Rep. 2013;11:31-41.
13. Rubio-Gozalbo ME, Haskovic M, Bosch AM, Burnyte B, Coelho AI, Cassiman D, et al. The natural history of classic galactosemia: Lessons from the galnet registry. Orphanet J Rare Dis. 2019;14(1): 86.
14. Böhles H, Wenzel D, Shin YS. Progressive cerebellar and extrapyramidal motor disturbances in galactosaemic twins. Eur J Pediatr. 1986;145(5):413-417.
15. Lo W, Packman S, Nash S, Schmidt K, Ireland S, Diamond I, et al. Curious neurologic sequelae in galactosemia. Pediatrics. 1984;73(3): 309-312.
16. Wang S, Lawson F, Perfetti R, Shendelman S. Progressive worsening of central nervous system phenotype in children with classic galactosemia: A cross-sectional analysis. Mol Genet Metab. 2021;132:S7-S8.
17. Bailey E, Wang S, Randall J, Sutter C, Raither L, Perfetti R, et al. Qualitative interviews of adults with Classic Galactosemia (CG) and their Caregivers: Disease burden and challenges with daily living. Int Congr Inborn Err Metab. 2021.
18. Bosch AM. Classical galactosaemia revisited. J Inherit Metab Dis. 2006;29(4):516-525.
19. Welling L, Meester-Delver A, Derks TG, Janssen MC, Hollak CE, de Vries M, et al. The need for additional care in patients with classical galactosaemia. Disability and rehabilitation. 2019 23;41(22): 2663-2668.
20. Waisbren SE. Speech and language deficits in early-treated children with galactosemia. J Pediatr. 1983;102(1):75-77.
21. Potter NL, Lazarus JA, Johnson JM, Steiner RD, Shriberg LD. Correlates of language impairment in children with galactosaemia. J Inherit Metab Dis. 2008;31(4):524-532.
22. Timmers I, van den Hurk J, Di Salle F, Rubio-Gozalbo ME, Jansma BM. Language production and working memory in classic galactosemia from a cognitive neuroscience perspective: Future research directions. J Inherit Metab Dis. 2011;34:367-376.

23. Bosch AM, Grootenhuis MA, Bakker HD, Heijmans HS, Wijburg FA, Last BF. Living with classical galactosemia: Health-related quality of life consequences. Pediatr. 2004;113(5):e423-8.
24. Hermans ME, Welsink-Karssies MM, Bosch AM, Oostrom KJ, Geurtsen GJ. Cognitive functioning in patients with classical galactosemia: A systematic review. Orphanet J Rare Dis. 2019;14:226.
25. Berry GT. Classic galactosemia and clinical variant galactosemia. Gene Rev. 2021.
26. Miller LT, Missiuna CA, Macnab JJ, Malloy-Miller T, Polatajko HJ. Clinical description of children with developmental coordination disorder. Can J Occup Ther. 2001;68(1):5-15.
27. Randall JA, Sutter C, Wang S, Bailey E, Raither L, Perfetti R, et al. Qualitative interviews with adults with classic galactosemia and their caregivers: Disease burden and challenges with daily living. Orphanet J Rare Dis. 2022;17(1):138.
28. Mason HH, Turner ME. Chronic galactemia: Report of case with studies on carbohydrates. Am J Dis Child. 1935;50(2):359-374.
29. Hughes J, Ryan S, Lambert D, Geoghegan O, Clark A, Rogers Y, et al. Outcomes of siblings with classical galactosemia. J Pediatr. 2009;154(5):721-726.
30. Waggoner DD, Buist NR, Donnell GN. Long-term prognosis in galactosaemia: Results of a survey of 350 cases. J Inherit Metab Dis. 1990;13(6):802-818.
31. Beigi B, O'Keefe M, Bowell R, Naughten E, Badawi N, Lanigan B. Ophthalmic findings in classical galactosaemia-prospective study. Br J Ophthalmol.1993;77(3):162-164.
32. Schadewaldt P, Kamalanathan L, Hammen HW, Wendel U. Age dependence of endogenous galactose formation in Q188R homozygous galactosemic patients. Mol Genet Metab. 2004;81(1): 31-44.
33. Berry GT, Nissim I, Lin ZH, Mazur AT, Gibson JB, Segal S. Endogenous synthesis of galactose in normal men and patients with hereditary galactosaemia. Lancet. 1995;346(8982):1073-1074.
34. Berry GT, Nissim I, Mazur AT, Segal SS. The rate of endogenous galactose synthesis in normals and patients with galactose-1-phosphate uridyltransferase deficiency 704. Pediatr Res. 1998;43(4):122.
35. Oh SL, Cheng LY, J Zhou JF, Henke W, Hagen T. Galactose 1-phosphate accumulates to high levels in galactose-treated cells due to low GALT activity and absence of product inhibition of GALK. J Inherit Metab Dis. 2020;43(3):529-539.
36. Liu Y, Xia B, Gleason TJ, Castaneda U, He M, Berry GT, et al. N- and O-linked glycosylation of total plasma glycoproteins in galactosemia. Mol Genet Metab. 2012;106(4):442-454.
37. Wehrli SL, Berry GT, Palmieri M, Mazur A, Elsas L, Segal S. Urinary galactonate in patients with galactosemia: Quantitation by nuclear magnetic resonance spectroscopy. Pediatr Res. 1997;42(6): 855-861.
38. Coelho AI, Rubio-Gozalbo ME, Vicente JB, Rivera I. Sweet and sour: An update on classic galactosemia. J Inherit Metab Dis. 2017;40(3):325-342.
39. Birlouez-Aragon I, Alloussi S. Effect of prolonged galactose consumption on galactose tolerance in young healthy humans. Ann Nutr Metab. 1990;34(1):1-7.
40. Singh M, Kapoor A, Bhatnagar A. Physiological and pathological roles of aldose reductase. Metabolites. 2021;11(10):655.
41. Arola H, Sillanaukee P, Aine E, Koivula T, Isokoski M.Galactitol is not a cause of senile cataract. Graefes Arch Clin Exp Optom. 1992;230:240-242.
42. Ning C, Segal S. Plasma galactose and galactitol concentration in patients with galactose-1-phosphate uridyltransferase deficiency galactosemia: Determination by gas chromatography/mass spectrometry. Metabolism. 2000;49(11):1460-1466.
43. Belman AL, Moshe SL, Zimmerman RD. Computed tomographic demonstration of cerebral edema in a child with galactosemia. Pediatr. 1986;78(4):606-609.
44. Conte F, van Buuringen N, Voermans NC, Lefeber DJ. Galactose in human metabolism, glycosylation and congenital metabolic diseases: Time for a closer look. Biochim Biophys Acta Gen Subj. 2021;1865(8):129898.
45. Hennermann JB, Schadewaldt P, Vetter B, Shin YS, Mönch E, Klein J. Features and outcome of galactokinase deficiency in children diagnosed by newborn screening. J Inherit Metab Dis. 2011;34(2): 399-407.
46. Daenzer JM, Jumbo-Lucioni PP, Hopson ML, Garza KR, Ryan EL, Fridovich-Keil JL. Acute and long-term outcomes in a Drosophila melanogaster model of classic galactosemia occur independently of galactose-1-phosphate accumulation. Dis Model Mech. 2016;9(11): 1375-1382.
47. Rasmussen SA, Daenzer JM, MacWilliams JA, Head ST, Williams MB, Geurts AM, et al. A galactose-1-phosphate uridylyltransferase-null rat model of classic galactosemia mimics relevant patient outcomes and reveals tissue-specific and longitudinal differences in galactose metabolism. J Inherit Metab Dis. 2020;43(3):518-528.
48. Leslie ND, Yager KL, McNamara PD, Segal S. A mouse model of galactose-1-phosphate uridyl transferase deficiency. Biochem Mol Med. 1996;59(1):7-12.
49. Leslie ND. Insights into the pathogenesis of galactosemia. Annu Rev Nutr. 2003;23(1):59-80.
50. Shendelman S, Perfetti R, Lawson F, Ghannam A. Post-natal galactitol reduction is associated with normalization of CNS phenotype in an animal model of galactosemia. ASHG. 2020.
51. Wells WW, Pittman TA, Wells HJ, Egan TJ. The isolation and identification of galactitol from the brains of galactosemia patients. J Biol Chem. 1965;240(3):1002-1004.
52. Quan-Ma R, Wells HJ, Wells WW, Sherman FE, Egan TJ. Galactitol in the tissues of a galactosemic child. Am J Dis Child. 1966;112(5):477-478.
53. Berry GT, Hunter JV, Wang Z, Dreha S, Mazur A, Brooks DG, et al. *In vivo* evidence of brain galactitol accumulation in an infant with galactosemia and encephalopathy. J Pediatr. 2001;138(2):260-262.
54. Otaduy MC, Leite CC, Lacerda MT, Costa MO, Arita F, Prado E, et al. Proton MR spectroscopy and imaging of a galactosemic patient before and after dietary treatment. AJNR Am J Neuroradiol. 2006;27(1):204-247.
55. Martinelli D, Bernardi B, Napolitano A, Colafati GS, Dionisi-Vici C. Teaching neuro images: Galactitol peak and fatal cerebral edema in classic galactosemia: Too much sugar in the brain. Neurology. 2016;86(3):e32-e33.
56. Huttenlocher PR, Hillman RE, Hsia YE. Pseudotumor cerebri in galactosemia. J Pediatr. 1970;76(6):902-925.
57. Litman N, Kanter AI, Finberg L. Galactokinase deficiency presenting as pseudotumor cerebri. J Pediatr. 1975;86(3):410-412.
58. Perfetti R, Bailey E, Lawson F, Wang S, Saltonstall L, Krumnow M, et al. Galactitol-but not gal-1p-level is a predictor of disease severity in children with classic galactosemia on galactose restricted diet. Int Congr Inborn Err Metab. 2021.