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Possible Treatment for the Arresting of Progression of Parkinson's Disease from Bovine Milk

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Abstract: An approach to study Ca^{+2} channel function using bovine milk component or a product (s) of milk components and $NaBH_4$ in NH_4OH. The successful study of these molecules could lead to their use in the treatment of Parkinson's disease or could lead to the use of bovine milk itself as a treatment for this disease. Bovine milk, a source of two molecules and itself, to be used to possibly block the progression of Parkinson's disease (PD) is reported. The structures of these molecules were established by ESI-MS and API-MS. There is ESI-MS support for the milk component and its product upon treatment with $NaBH_4$ in NH_4OH. A mechanism for the possible rescue of Ca^{+2} channel function is proposed to include a Tyr-Asn (Asp) dipeptide requirement in calcium channels and that it requires the incorporation of N-acetamido neuraminic acid, and SO_4^- residues as well, for the restoration of calcium channel function. If one or both molecules effectively rescue Ca^{+2} channel function, an inexpensive treatment of Parkinson's disease could be available by either simply drinking milk or a treatment could be available via a simple process using bovine milk as its source. A possible treatment of PD, because of the projected low cost, would be available to those less fortunate in the third world.

Keywords: Bovine Milk Component, $NaBH_4/NH_4OH$ Treatment, Mass Spectrometry, Parkinson's Disease, Proposed Mechanism of Ca^{+2} Channel Function

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease affecting some seniors or those in contact sports. The etiology of PD includes channelopathy including calcium channel aberration. [1] It is known that calcium channel blockers can produce Parkinson's disease. A mutation of an asparagine residue lacks calcium channel function but can be restored with inclusion of GM3 in the cell membranes. [2] The structure of GM3 includes an N-acetamido neuraminyl lactose epitope linked to sphingosine. Yet GM1 does not rescue calcium channel function when incorporated into cell membranes. [2]

Snail venom toxins exert their channel dysfunction and have a conserved dipeptide, Tyr-Asn (Asp) in their polypeptide structure. [3-4] A dipeptide linked to an oligosaccharide may act in a capacity to assist in targeting this molecule to the dysfunctional calcium channel. Such a molecule is found in bovine milk. [5-6] It is N-acetamido neuraminyl galactosyl phospho glucosyl di-phospho asparaginyl sulfo tyrosine dipeptide. [6] Another molecule may act in this manner and is isolated from bovine milk. [6] It carries the di-phospho asparaginyl sulfo tyrosine dipeptide which could act as a targeting residue for arresting calcium channel dysfunction. [6, 7] Omega conotoxin from snail venom is known to contain in its structure, an O-linked oligosaccharide linked to serine and an N-linked oligosaccharide. [8, 12] It contains no N-acetamido neuraminyl group or Tyr-SO_4^-, which could possibly be involved in shuttling calcium through a calcium channel. This toxin results in channelopathy. It is postulated that the N-acetamido neuraminyl epitope is required to maintain calcium channel function.

Therefore to restore calcium channel function both Tyr-Asn (Asp) functionality and terminal N-acetamido neuraminyl group is, possibly, necessary. Thus the noted molecules from bovine milk, both the oligosaccharide sulfo

dipeptide and the 1,5 anhydro trisaccharide, could be important in blocking the progression of calcium channel dysfunction. The importance of the di-phospho asparaginyl sulfo tyrosine portion of the molecule from bovine milk could be determined by the use of both molecules in a model system used to study human calcium channel function. For the bovine milk oligosaccharide dipeptide one may be directed to the preparative method found in a recent report. [7] Its preparation is noted in the materials and methods section, as well. The method for the preparation of the 1,5 anhydro N-acetamido neuraminyl galactosyl phospho glucose is also found in the materials and methods section.

2. Materials and Methods

2.1. Preparation of Bovine Milk Trisaccharide Dipeptide

Bovine milk (1.0 mL) is extracted with 95% ethanol (10.00 mL). The mixture is centrifuged and the supernatant collected. The ethanol is removed by a stream of N_2. This can be diluted to an appropriate volume with H_2O. [7] The mixture was partially thawed prior to analysis by a single quadrapole mass spectrometer, in the negative ESI-MS mode. [6, 7]

2.2. Preparation of Bovine Milk 1,5 Anhydro Trisaccharide

Bovine milk 1,5 anhydro oligosaccharide was prepared in the following manner; bovine milk (0.1 mL) is diluted with H_2O (1.00 mL). The mixture is pushed through a NH_4^+ cation exchange cartridge (ThermoFIsher, Sunnyvale, CA USA). The effluent is collected and evaporated to no less than 0.200 mL. To this solution is added NH_4OH (1.00 mL, pH 11.4, 1N). Then $NaBH_4$ (0.003 mL of a, 4N solution) is added. The mixture is allowed to stand at ambient temperature for 2 hours, capped. The reaction mixture was pushed through an NH_4^+ form cation exchange cartridge (ThermoFisher, Sunnyvale CA, USA). The effluent was evaporated to no less than 0.20 mL. This chemistry is also documented in the literature. [13-15] The mixture was frozen, and thawed for analysis by a triple quadrapole API 2000, in the negative mode. [6, 7]

3. Results and Discussion

The target for the rescue of calcium channel is novel. With an appropriate model for testing Ca^{+2} channelopathy rescue these two compounds could light the way for of bovine milk to treat calcium channel dysfunction and its function in Parkinson' disease.

Found in Figure 1 is a cartoon for the possible target for rescue of this channelopathy. The proposed model would suggest that the Asn-Tyr dipeptide could act as a director of bovine milk oligosaccharide dipeptide. It may bring the sialyl lactose component into the vicinity where GM3 sialyl lactose may have acted. This targeting hypothesis could be tested by using the 1,5 anhydro oligosaccharide from bovine milk.

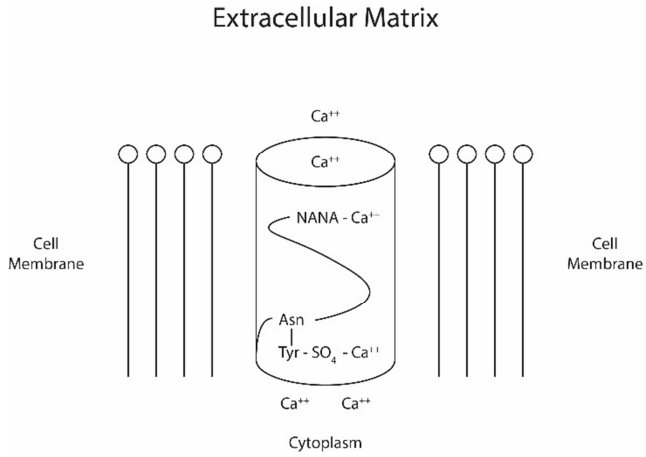

Figure 1. *Model of how bovine milk oligosaccharide dipeptide may arrest progression of Parkinson's disease channelopathy Shown in Figure 2 is the mass spectrum for the isolated milk oligosaccharide dipeptide. Figure 3.*

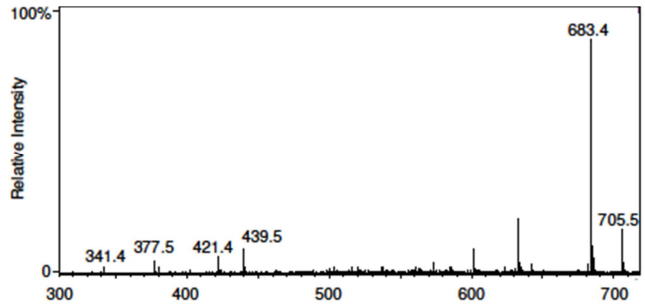

Figure 2. *ESI-MS negative mode mass spectrum of bovine milk oligosaccharide dipeptide.*

Its structure is shown in Figure 3. The Asn-Tyr is evident in this structure.

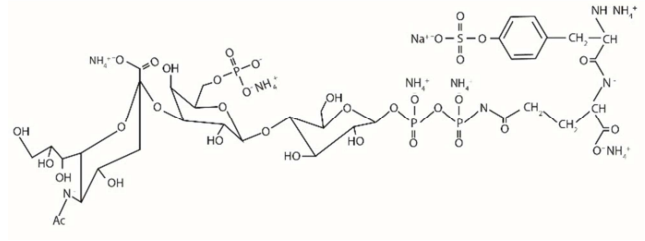

Figure 3. *Bovine milk ethanol extract, phospho trisaccharide di-phospho asparaginyl sulfo tyrosine dipeptide.*

Drawn in Figure 4 is the structure for the 1,5 anhydro oligosaccharide.

As noted this molecule has no di-phospho dipeptide component.

Picture in Figure 1 is the model for how bovine milk oligosaccharide dipeptide may facilitate if not rescue Ca^{++} channel function. The Asn-Tyr linkage in bovine milk molecule may serve as a 'homing deliverer' of Ca^{++} for binding N-acetamido neuraminic acid moiety in order to facilitate transfer of this in to the cell's cytoplasm. To test this hypothesis the 1,5 anhydro milk oligosaccharide could be used.

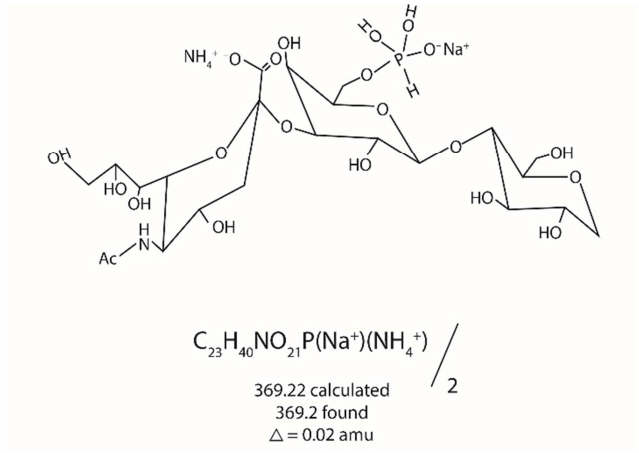

Figure 4. *Structure of the milk oligosaccharide treated with $NaBH_4$ in NH_4OH.*

It is supported by the ms spectrum in Figure 5.

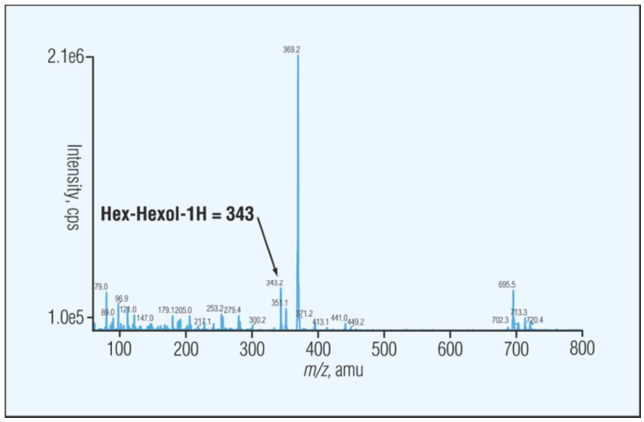

Figure 5. *API-MS of molecule obtained from treatment of bovine milk with $NaBH_4$ in NH_4OH for two hours capped.*

Nor would the sulfate anion, esterified to the tyrosine residue in the original molecule, be available to, presumably, assist in the transfer of Ca^{+2} to the cell cytoplasm. Because sulfate ester is a weaker base, Ca^{+2} is released much more readily than the N-acetamido neuraminic acid anion. It is not known how calcium bound N-acetamido neuraminic acid anion releases Ca^{+2} to the cytoplasm. The mechanism may include a gradient of Ca^{+2} ion concentrations across the channel. The calcium would be at higher concentration outside the cell than inside the cell, which could provide the force necessary to shuttle Ca^{+2} to NANA and to the SO_4^- and then into the cell cytoplasm.

The orientation of a possible epitope that rescues or arrests progression of Ca^{+2} channel dysfunction is as shown in Figure 1. The NANA (N-acetamido neuraminic acid) portion is drawn near the outside of the calcium channel. The sulfated tyrosine would be located in the channel facing the cytoplasm of the cell. The carboxylate anion is more basic than the sulfate on tyrosine. This orientation would be optimal because the capture of Ca^{+2} by NANA carboxylate could compete better for Ca^{+2}, near the outside of the cell, than would sulfate. The Ca^{+2} transferred to sulfate in the channel would release it more readily than another carboxylate such as NANA carboxylate. Another carboxylate, such as from an amino acid, tricarboxylate, uronate or an internal NANA carboxylate would readily receive the sulfate's ionically bound Ca^{+2}, because they have higher pKas than sulfate anion. These pKas indicate more basicity than sulfate anion.

Along with the 1,5 anhydro oligosaccharide, which could be used to investigate the importance of the Asn-Tyr portion of the bovine milk molecule, the ethanol extract of bovine milk could be used to mitigate the progression of Parkinson's disease and point to the use of bovine milk itself as a treatment for this disease.

4. Conclusion

With this novel model of calcium channelopathy rescue the potential role of the Asn-Tyr residue would have in targeting the rescue epitope of sialyl lactose, using the bovine milk direct isolate could be investigated. And the N-acetamido neuraminyl epitope linked to galactosyl phospho glucosyl di-phospho asparaginyl sulfo tyrosine, could also be investigated. The 1,5 anhydro sialyl lactose could be helpful in this endeavor. This could eventually lead to three possible treatments for arresting the progression of Parkinson's disease. The treatments could include bovine milk itself. Clearly these compounds could be used to mitigate Ca^{+2} channel function, to rescue it or to modulate it. Calcium channelopathy in Parkinson's disease could be studied with these compounds, three maybe four, compounds. The importance of Ca^{+2} function in arresting progression of Parkinson's disease could be known using these molecules. With an inexpensive treatment for Parkinson's disease, derived from bovine milk, those in the third world would have greater access to possibly effective treatment for this disease. It would impart dignity and self-worth to those forgotten by the world's system.

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