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REVIEW ARTICLE

Nephrogenic diabetes insipidus: potential treatments and their mechanisms of action.

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Abstract:

Nephrogenic diabetes insipidus (NDI) is a rare disease caused by the complete or partial resistance of the kidneys to antidiuretic hormone (ADH). NDI associated with excessive urine production and severe thirst. There are two types of NDI; acquired NDI and congenital NDI. Acquired NDI is the most common type among adults, with several factors that can cause acquired NDI, for instance, lithium therapy and electrical disorders. Congenital NDI can occur due to mutations in either the arginine vasopressin receptor 2 (AVPR2) gene or the aquaporin-2 (AQP2) gene. New effective treatments for NDI are required because the disease can be life treating if left untreated. Current animal studies showed that rolipram and metformin are two potential treatments for congenital NDI by upregulation the apical expression of AQP2 channels. Other animal studies illustrated that the combination of different drugs, such as, secretin agonist and fluvastatin could be an effective method to treat XNDI. Furthermore, some agents were found to be able to treat more than one type of NDI, for example, sildenafil citrate could be potently used to treat acquired NDI and XNDI, while statins could be promising treatments for congenital NDI and autosomal NDI. However, further investigation and human trials are needed before it can be decided if these drugs can be clinically used as a treatment for NDI.

Keywords: Aquaporins, Nephrogenic diabetes insipidus, AQP2, Statins, Secretin agonists

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INTRODUCTION:

Nephrogenic diabetes insipidus (NDI) is a rare disorder characterized by the production of large quantities of dilute urine, around 12 L/day, due to failure of the renal tubules to respond to the action of antidiuretic hormone (ADH) [(1)]. There are two forms of the NDI; acquired NDI, which is more common in adults, and congenital NDI[(2)]). Moreover, the symptoms of NDI will vary from mild to severe between patients. The main symptoms of NDI are polyuria and polydipsia. NDI can be life threating if left untreated since it leads to severe dehydration[(3)]. There are different approaches to treat NDI, for instance, specific diet to reduce the osmotic load, administration of hypotonic fluids, and pharmacological interventions[(4)]. This essay will include a brief description about NDI, then it will describe some new possible therapeutic approaches and their mechanisms of action.

Congenital NDI:

Congenital NDI can be divided into 2 types: XNDI and autosomal NDI. XNDI is caused by mutations in the arginine vasopressin receptor 2 (AVPR2) gene, which encodes for V2 receptor[(5)]. There are around 274 known mutations in AVPR2 gene that lead to XNDI, these mutations are categorized into five classes (Table1)[(6,7)] .The majority of these mutations produce misfolded V2 receptor proteins, which cannot reach the apical membrane and cannot interact with ADH. At birth, the urine concentrating defect is present, and most of the symptoms arise during the first weeks of life[(8)].

Moreover, around 10% of patients with congenital NDI have mutations in aquaporin-2 (AQP2) gene, which encodes for AQP2 water channels which lead to autosomal NDI(4). At the moment, 65 mutations in AQP2 gene have been found to cause autosomal NDI including missense, splicing, small deletions and small insertions (Figure 1)[(6)]. Theses mutations, such as AQP2-R254W, can prevent the fusion of AQP2 channels with the apical membrane by retain the cannels in the intracellular space[(9)]. Leading to decrease in the expression of AQP2 cannels. The mutations can also inhibit the function of AQP2 channels via disturbing the formations of pore-forming structure of AQP2 cannels[(10)].

Table 1: Classficatin of AVPR2 mutaions that lead to nephrogenic diabetes insipidus (NDI).The table is adopted and updated from from Wesche et al.[(7)]

Class	Mechanism	Mutation type	Examples
I	Interference with transcription, mRNA processing, translation	Missense, splice site, frame-shift, early nonsense	W71X, 458delG
II	Aberrant folding and intracellular (ER) retention	Missense, in-frane del/ins, last exon nonsense	S167T
IIIa	Loss of G-protein-binding site	Missense	D85N, P322S
IIIb	Loss of AVP- binding site	Missense	delR202
IV	Defects in intracellular trafficking	Missense	R127H

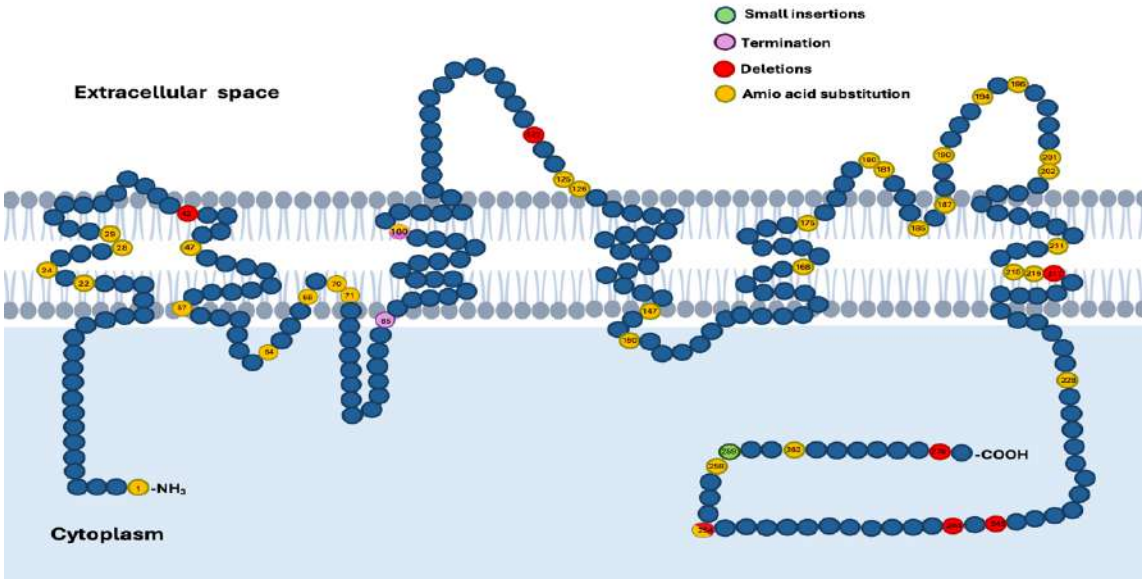

Figure 1: The structure of AQP2 protein and the location of some of the mutations linked to congenital NDI. Diagrams is adopted and updated from Moeller *et al.*[8]

Acquired NDI:

Acquired NDI syndromes are the most common forms of NDI, which can decrease water reabsorption by either reducing the expression of AQP2 channels in the apical membrane, or by disturbing AQP2 trafficking to the apical membrane [5]. They are different factors that can cause acquired NDI, for instance, lithium therapy, hypokalemia and hypercalcemia. Approximately 40% of individuals who were treated with lithium salts developed lithium-induced NDI. High concentrations of lithium within principal cells can reduce the levels of AQP2 in the apical membrane by around 90%[5] .The downregulation AQP2 expression levels may also be caused by both hypokalemia and hypercalcaemia. It should be highlighted that hypercalcaemia was found to have an effect on the expression of AQP1 and AQP3 as well[8].

Treatments:

TREATMENTS:

Statins

Statins, including simvastatin and atorvastatin, are commonly used inhibitors of cholesterol biosynthesis. Simvastatin was found to significantly increase the expression of AQP2 mainly in the collecting duct located in the cortex and outer medulla in animal models with autosomal NDI[11]. Recent study showed that atorvastatin administration can upregulate the accumulation of AQP2, which lowers the risk of developing NDI among lithium users from 20% to almost 0%[12].Another study illustrated that, the administration of fluvastatin for 90 days increased the accumulation of AQP2 in patients with XNDI. However, neither a reduction of diuresis nor increase of urine osmolality were obtained[13].

Statins mode of action was thought to be due to reduction of endocytosis of AQP2, increasing exocytosis, or both. However, vitro experiments illustrated that statins mechanism of action is only due to the reduction of endocytosis of AQP2, which is achieved by preventing cholesterol synthesis and lowering cholesterol content of cells mainly in the plasma membrane. Satins can also inhibit the activity of leading to down regulation of clathrin-mediated endocytosis, so the expression of AQP2 rapidly increase[11].

Statins are well-tolerated and suggested to have few side effects on cognition and mood. Statins have some positive effects on cardiovascular risk prevention. Although statins are considered as promising treatment for lithium-induced NDI and autosomal NDI, further investigations are required to test their effect on XNDI.

Secretin agonists

Secretin receptors are G‑protein coupled receptors expressed in the basolateral membrane of CD principal cells[6]. A current animal study showed that the activation of secretin receptors in AVPR2-KO mice elevated the abundance of AQP2, mainly because the stimulation of secretin receptors can activate adenylyl cyclase, which increases intracellular cyclic adenosine

monophosphate (cAMP) levels and activate protein kinase A and (PKA) and eventually phosphorylate AQP2[14]. Therefore, secretin receptors can mimic the activity of AVPR2. However, the activation of secretin receptors had no effect on the apical expression AQP2.

The same study illustrates that when secretin and small amount of fluvastatin were injected to the mice, the urine output decreased by around 90% and the urine osmolality was doubled[14]. Thus, it can be assumed that a combination of secretin agonist and fluvastatin can be a potential treatment for XNDI.

Metformin:

Metformin, which is a current treatment for type 2 diabetes, was found to be able to increase the accumulation of AQP2 in the apical membrane by activating adenosine monophosphate kinase (AMPK) which phosphorylates AQP2 and elevates osmotic water permeability in XNDI rats model[15]. In the same study metformin increased urea permeability by the activation urea transporter UT-A1 via AMPK. Additionally, in a different animal study the stimulation of AMPK via metformin results in rising the expression of Na-K-2Cl cotransporter (NKCC2) in outer medulla by 117%, and the accumulation of AQP2 and UT-A1 by 44% and 61% respectively[16]. The upregulation of NKCC2 makes the medulla hypertonic and generates the osmotic gradient, which acts as water reabsorption[15].

It should be highlight that, metformin was shown to be only able to increase urine-concentrating ability, when V2 receptors were blocked or knocked out in mice. Therefore, it is believed that metformin could be a novel treatment for congenital NDI resulting from AVPR2 mutations.

Phosphodiesterase (PDE) inhibitors

Normally the interaction between ADH and V2 receptors stimulates cAMP-mediated activation of PKA and activates AQP2 channels[8]. Rolipram, a PDE4 inhibitor, can mimic the effect of ADH and elevate cAMP levels which in turn activate AQP2 channels and raise the expression of the channels in the apical membrane. An animal experiment illustrated that the administration of rolipram significantly increased urine osmolality in heterozygous mutant AQP2 knockin mice[17]. Therefore, rolipram should be considered as a treatment for autosomal NDI.

Sildenafil citrate is a PDE5 inhibitor also known as Viagra, was proven to be able to rise the expression of AQP2 channels in rats with Li-induced NDI, by increasing the intracellular cGMP levels and inhibiting the degradation of Cgmp .As a result water reabsorption increased and urine output dramatically decreed[18]. Even though in Sohara *et al*.[17] experiment sildenafil slightly decreased urine osmolality in AQP2 mutant mice, in recent case study sildenafil elevated both urine osmolality and the accumulation of AQP2, and reduced urine output in 4 years old patient with XNDI[19]. Therefore, the usage of sildenafil should be considered as threptic approach to treat patients with either XNDI or Li-induced NDI.

CONCLUSION:

In conclusion, nephrogenic diabetes insipidus (NDI) is a rare disease develops when there is a lack of respond to ADH in the kidneys, the main symptoms are polyuria and polydipsia. There are two types of NDI; acquired NDI and congenital NDI. Current studies found that new possible treatments can be used to treat different types of NDI, such as rolipram and metformin which were shown to be able to treat congenital NDI. A combination of secretin agonist and fluvastatin could provide a promising therapeutic approach for XNDI. Moreover, some agents could treat different types of NDI; sildenafil citrate could be potently used to treat acquired NDI and XNDI, whereas statins could be a novel treatment for congenital NDI and autosomal NDI. However, some human trials are required before it can be concluded which of these drugs can be clinically used as a treatment for NDI.

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