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A New Concept for the Regulation of Electrolytes in Pregnancy: The Role of Ionotropin, the Endogenous Potassium Sparing Hormone

Fred Chasalow*

IOMA LLC, California, USA

***Corresponding Author:** Fred Chasalow, IOMA LLC, California, USA.

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Abstract

During pregnancy, there are characteristic changes that occur in electrolytes. The most obvious difference is that during pregnancy all nutrition is provided via the placenta, but after parturition, nutrition is provided mostly by mother's milk. The two fluids differ significantly in their electrolyte composition. In brief, during the 3rd trimester, potassium must be accumulated in the fetal tissues and sodium ions must be delivered to the amniotic fluid. After parturition, when milk-based nutrition begins, the need to conserve potassium ends and the need to prevent sodium wasting begins. There has been no satisfactory explanation for the endocrine mechanism that regulates the switchover from high sodium levels during gestation to high potassium levels from milk after parturition. Recently, we have discovered a novel steroid, which we named Ionotropin. It functions as an endogenous potassium sparing hormone. This paper presents a new concept. Ionotropin regulates electrolytes during pregnancy and the neonatal period. Changes in Ionotropin levels are responsible for both processes.

Keywords: *Ionotropin; Aldosterone Signaling Defects; Aldosterone Resistance; Potassium Sparing Hormones; DLM*

Abbreviations

DLM: Unidentified Materials that cross react with digoxin specific antibodies; ENaC: Epithelial Sodium Channel; K^+: Potassium Cation; Na^+: Sodium Cation; SLOS: Smith-Lemli-Opitz Syndrome-7-Dehydrosterol Reductase Deficiency

Introduction

Type of submission – New Concept Paper

Ionotropin is a newly discovered steroid hormone that shares structural analogy with spironolactone, a potassium-sparing synthetic steroid [1]. This paper briefly reviews the physiology of electrolyte regulation during pregnancy and describes the possible function of Ionotropin in this process.

Physiology

During pregnancy, the electrolytes needed by the fetus are provided by the placental circulation. The 'feedstock' resembles maternal plasma, high in Na^+, low in K^+. In early pregnancy, in the fetus, aldosterone binds to the mineralocorticoid receptor and directs the synthesis of ENaC, limiting fetal Na^+ wasting. During the 3rd trimester the situation changes. First, synthesis of ENaC is restricted and then synthesis of aldosterone declines. In toto, aldosterone synthesis is minimal and what aldosterone is made, doesn't signal at the mineralocorticoid receptor [2]. During this period, the kidney effluent forms the amniotic fluid. Amniotic fluid electrolytes are tightly regulated, in contrast to urinary electrolytes, which vary depending on dietary intake.

At parturition, the situation changes. The 'feedstock' is mother's milk, which may be supplemented by animal or plant 'milks', if necessary. Milk is much richer in K^+ and poorer in Na^+ when compared to the maternal plasma. Initially, a newborn infant is Na^+ wasting and loses about 10% of its weight. The weight loss is mostly extracellular fluids with electrolyte composition similar to that of serum. When the weight and Na^+ loss end, growth resumes, usually at 1 - 2 weeks of post-natal age. The process that causes weight loss and the biochemical changes that lead to its termination are unknown.

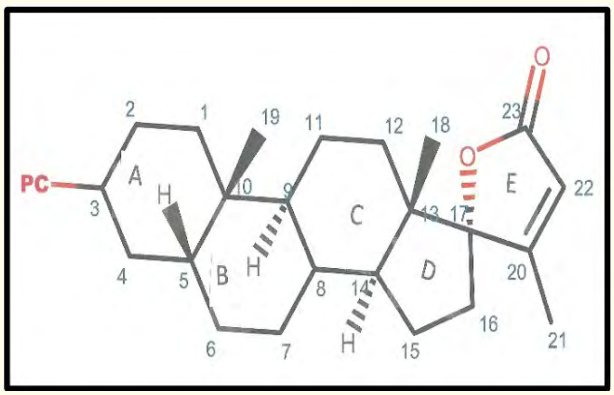
Initial observation of DLM

In the beginning, there was digoxin, a drug that was hard to administer because it had a narrow therapeutic index. Investigators responded by developing an immunoassay for digoxin [3]. Digoxin levels below 0.6 ng/mL were inadequate but levels above 1.8 ng/mL were associated with digoxin toxicity. Physicians routinely ordered a digoxin assay prior to therapy and monitored therapy with additional assays. The assay had a detection limit of 0.15 ng/mL. From time to time, samples were identified with detectable digoxin levels before digoxin therapy. The situation changed when an infant died with heart failure and the clinical laboratory detected significant values of digoxin. The nurse was accused of murder for administering digoxin without the instruction of a doctor [4]. This was the first indication of unknown materials that are detected by digoxin-specific assays, commonly designated as DLM.

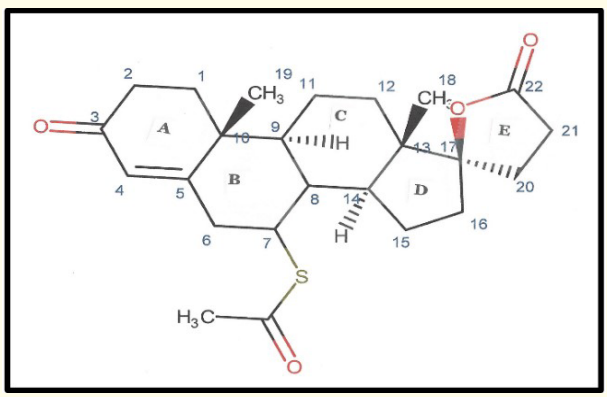
Over the years, more than 200 papers and presentations (including 7 from this author) described patients with DLM and/or attempted to determine the identity of the DLM [5].

Biochemistry of Ionotropin

Ionotropin is a newly discovered steroid hormone [1]. It is the phosphocholine ester of a previously unknown steroid. The steroid has a molecular weight of 358 Da. A trial and error analysis identified only one formula consistent with 358 Da – $C_{23}O_4H_{34}$. There are no other mammalian examples of a steroid with 23 carbon atoms or of a steroid phospho-choline ester. Initially, Ionotropin was isolated by assaying individual column fractions for DLM. In addition to Ionotropin, several potential precursors were identified and a pathway from known compounds to Ionotropin was identified. There were no other unknown DLM in the extracts or column fractions. Ionotropin shares structural features with spironolactone and digoxin. All three compounds have lactone rings attached to the usual 4-ring structure of steroids (Figure 1). What is unique about this pattern is that for all other steroid hormones, the natural hormone was discovered before synthetic compounds were made. For this hormone the reverse is true. The synthetic was discovered in the 1950s and Ionotropin, the endogenous hormone, was described in 2018.



Top: The proposed structure of Ionotropin. Note the similarity of the A and B rings of Ionotropin and digoxin and of the D and E rings of spironolactone and Ionotropin.



Bottom: The structure of spironolactone. Note the similarity of the E-ring.

Function of Ionotropin

Two clinical observations support the hypothesis of Ionotropin as the endogenous potassium sparing hormone. First, the biosynthesis pathway to Ionotropin includes 7-dehydrosterol reductase. Patients with a defect in this enzyme (Smith-Lemli-Opitz Syndrome-SLOS) are potassium wasting, as would be expected if the function of Ionotropin stimulated potassium recovery in the kidney, and if an inborn error prevented the synthesis of Ionotropin [6]. Second, there are two types of human breast cyst fluids: Type 1 with high K^+ levels and Type 2 with modest K^+ levels. Ionotropin was isolated from the Type 1 fluids, but it was not present in the Type 2 fluids [7]. This observation suggests Ionotropin causes K^+ accumulation against a concentration gradient. Spironolactone interferes with aldosterone binding to the mineralocorticoid receptor, leading to decreased synthesis of ENaC. Digoxin modulates NaK-ATPase activity, leading to K^+ transport against the gradient. Ionotropin seems to have both activities.

Digoxin and ouabain are both reported to be inhibitors of Na^+ transport, but inhibition of Na^+ transport has the same consequence as activation of K^+ transport (Is the glass half-full or half empty?). There seems little need for an ATP dependent process to transport Na^+ into a cell as that process is already driven by the existing gradient from high Na^+ in the extracellular fluids to the low levels in the intracellular fluid. What is needed is a sodium channel, such as ENaC.

There are two types of synthetic potassium sparing diuretics: (1) amiloride and triamterene block ENaC synthesis and (2) spironolactone and eplerenone are aldosterone antagonists. ENaC provides an enhanced channel for diffusion of Na^+ in both directions. The NaK-ATPase pumps K^+ into the cells and Na^+ into the extracellular fluid. If one discovered a novel steroid with an aromatic A-ring, one might expect it would function as an androgen. As spironolactone and Ionotropin share structural features (a 5-member lactone ring attached at carbon 17), the authors propose both compounds have similar functions: (a) regulation of the NaK-ATPase and (b) an aldosterone antagonist.

Concept

With this background, this paper explores the concept of Ionotropin as the key regulator of electrolytes during pregnancy. A preliminary report of this concept has been presented [8].

Materials and Methods

Cord serum samples were obtained by double clamping of the umbilical cord and withdrawing an arterial sample by syringe. If the concentration of hCG was greater than 50 mIU/mL, it was assumed the sample was contaminated by maternal venous plasma and discarded [9]. Digoxin-like materials (DLM) were evaluated with reagents obtained from Dupont, Cambridge, MA [7]. The DLM in cord serum [10] co-eluted with the Ionotropin obtained from porcine blood (*Sus scrofa domesticus*) which we recently purified to homogeneity; its chemical formula was determined on the basis of its molecular weight. The authors assigned the trivial name, Ionotropin, based on its apparent function to regulate electrolytes [1].

Results and Discussion

DLM in women during pregnancy

Graves showed that most pregnant women had DLM in their serum [11]. The levels were higher as gestation proceeded and were even higher in women who developed pre-eclampsia [12]. At parturition, DLM was typically 0.1-0.2 ng/mL in the maternal circulation but exceeded 0.4 ng/mL in more than half of the women with eclampsia [12, 13]. During pregnancy, there are three possible sites of synthesis of Ionotropin: maternal adrenal, fetal adrenal and the placenta.

K+ levels during pregnancy

There are two unusual features of K^+ levels during pregnancy: (1) during the period of rapid fetal growth, the fetal cells must accumulate K^+. Serum K^+ levels in fetal serum are 6 mM compared to maternal levels of 4 - 5 mM. However, intracellular levels are 100 mM. There must be a mechanism to pump K^+ against that gradient to get K^+ into cells. (2) As the fetus grows, blood pressure must increase to maintain adequate profusion. Both of these features are functions of synthetic potassium sparing diuretics and would be expected to be functions of an endogenous potassium sparing hormone, such as Ionotropin.

The new concept is that if the fetus has an inadequate source of K^+ or inadequate perfusion, the fetus synthesizes Ionotropin as a messenger to the mother to increase placental K^+ levels. This would be the basis for the increase in maternal Ionotropin levels as gestation proceeds.

Na^+ levels during pregnancy

During the third trimester, a fetus has both hypo-aldosteronism and pseudo-hyper-aldosteronism. That is, synthesis of aldosterone is reduced and what is made, doesn't induce synthesis of ENaC at the mineralocorticoid receptor [2]. Ionotropin, like spironolactone, is an aldosterone antagonist and reduces signaling at the mineralocorticoid receptor. The absence of ENaC leads to less recovery of Na+ from the reformed plasma and provides Na^+ for the amniotic fluid.

Measurement of DLM and Ionotropin in cord serum

Chasalow and Blethen characterized the DLM in cord serum [10]. The DLM was very polar and solvent extraction easily separated the DLM from cardiac glycosides, such as ouabain or digoxin. There was little, if any, DLM that was not extracted with the solvents used. The extract containing the DLM was chromatographed and fractions analyzed by immunoassays with specificity for steroid sulfates, androgens and digoxin. There were 4 peaks on the chromatogram, but only 3 of the peaks were detected with the DLM assay. We now know that these four peaks were steroid phosphocholine esters [1].

Measurement of Ionotropin in the immediate post-partum period

Cord serum had DLM levels of 0.5 ng/mL and corresponding levels in all 4 of the steroid phosphocholine esters. By 2 weeks of age, the DLM was undetectable and the 4 phosphocholine steroid esters had dropped to the levels shown by older children [13].

Electrolytes in the first two weeks of life

The time course of neonatal adaption to aldosterone is divided into three phases. In the first week of post-natal life, Ionotropin levels are high, salt-wasting continues, but now the salt is 'wasted' in the urine, rather than becoming the base for the amniotic fluid, even though aldosterone levels are within the expected range. As a consequence, infants typically lose about 10% of their body weight. The second phase is a transitional week. The infant accommodates to the high levels of K^+ in milk, rather than the 5 mM levels of K^+ from the placenta. K^+ recovery is no longer needed and Ionotropin synthesis decreases to adult levels. After the transition, the adult phase begins. Aldosterone signaling is no longer blocked by Ionotropin, ENaC is synthesized, salt wasting ends and growth resumes. In summary, salt-wasting in newborn infants can't be attributed to hypoaldosteronism but could be caused by an aldosterone antagonist that disappears from the circulation during a short transition period. Ionotropin fits that pattern.

Within a month after delivery, most women have undetectable levels of DLM but the levels of Ionotropin are easily detected by LC-MS. This points to the placenta, the fetal adrenal or both, rather than the maternal adrenal, as the source of the high levels of Ionotropin.

Conclusion

Modest increases in fetal Ionotropin levels during the third trimester probably are the signal of the fetus for more K^+. Ionotropin is an antagonist at the mineralocorticoid receptor with the consequence that aldosterone signaling at the receptor is blocked. This reduces synthesis of ENaC, leading to less Na^+ being recovered from the nascent urine and returned to the fetus. The unrecovered electrolytes become the base for the amniotic fluid.

At parturition, Ionotropin synthesis by the fetal adrenal-placenta complex declines and is metabolized over the first week. In its absence, aldosterone signaling resumes, ENaC is synthesized and Na^+ wasting comes to an end. While the Na^+ wasting is occurring, the newborn loses weight. As the nutrition changes from the placenta to breast milk, the need to recover K^+ decreases, leading to decreased Ionotropin synthesis, aldosterone signaling resumes, Na^+ wasting ends and growth resumes.

In summary, Ionotropin is the key hormone that controls electrolyte metabolism during pregnancy and during the immediate post-natal period. Ionotropin acts as the endogenous potassium sparing hormone, a function that has not previously been described in mammals.

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Conflicts of Interest

No funding from any source.

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