Medical Hypotheses 102 (2017) 23–27

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

The role of aquaporins in polycystic ovary syndrome – A way towards a novel drug target in PCOS

Agata Wawrzkiewicz-Jałowiecka [a,*], Karolina Kowalczyk [b], Dagmara Pluta [b], Łukasz Blukacz [b], Paweł Madej [b]

[a] Department of Physical Chemistry and Technology of Polymers, Faculty of Chemistry, Silesian University of Technology, 44-100 Gliwice, Ks. M. Strzody 9, Poland
[b] Department of Gynecological Endocrinology, Medical Faculty in Katowice, Medical University of Silesia, 40-752 Katowice, Poland

ARTICLE INFO

Article history:
Received 19 October 2016
Accepted 5 March 2017

Keywords:
Aquaporins
Polycystic ovary syndrome
AQPs-oriented obesity treatment
Folliculogenesis
Follicular atresia

ABSTRACT

Aquaporins (AQPs) are transmembrane proteins, able to transport water (and in some cases also small solutes, e. g. glycerol) through the cell membrane. There are twelve types of aquaporins (AQP1–AQP12) expressed in mammalian reproductive systems. According to literature, many diseases of the reproductive organs are correlated with changes of AQPs expression and their malfunction. That is the case in the polycystic ovary syndrome (PCOS), where dysfunctions of AQPs 7–9 and alterations in its levels occur.

In this work, we postulate how AQPs are involved in PCOS-related disorders, in order to emphasize their potential therapeutic meaning as a drug target. Our research allows for a surprising inference, that genetic mutation causing malfunction and/or decreased expression of aquaporins, may be incorporated in the popular insulin-dependent hypothesis of PCOS pathogenesis. What is more, changes in AQP's expression may affect the folliculogenesis and follicular atresia in PCOS.

Introduction

Aquaporins (AQPs) are transmembrane proteins, which are able to transport water molecules (and in some cases also small uncharged molecules, as glycerol) through biological membranes [1–4]. AQPs are often divided to two classes, on the base of their permeability characteristics – aquaporins conducting only water (AQP0, AQP1, AQP2, AQP4, AQP5, AQP6, AQP8) and aquaglyceroporins, which are able to transport also small uncharged solutes e.g. glycerol (AQP3, AQP7, AQP9, AQP10) [5]. The remaining two groups: AQP11 and -12, are functionally distant from all the others [6]. Aquaporins are widely distributed in living organisms and in mammals – so far, 13 different types have been detected (AQP0–AQP12) [6]. They are expressed in broad range of organs: blood and lymphatic vessels, pancreas, secretory granules, airway and lungs, organs in reproductive systems, eye, ear, etc. They are not restricted to a sole tissue, but their expression depends on the certain cell type of a given organ, which directly reflects their functional role in that localization [4,6].

Considering female reproductive system, to date, the expression of 12 isoforms of aquaporins has been evidenced [7]. They have been found in vagina [8] and cervix – in cervical carcinoma cells and HPV transformed cells [9]. Aquaporins in endometrial cells play role in its' proliferation, receptiveness, endometriosis and carcinoma invasion, as well [10]. Few of them have been found to be responsible for water balance in human placenta and fetal membranes [11]. In the ovary, AQPs: 1–4 and 7–9 are localized, among others, in granulosa cells (GC) [7,12]. The presence of AQPs 1–4 in GC is important for normal ovulation process: in its early phase, the expression of AQP4 decreases, AQPs 2 and 3 are involved in the follicle rupture and, finally, AQP1 level increases in late ovulatory and postovulatory phase.

Due to their ubiquitous expression, high permeability and selectivity, AQPs are involved in a large number of processes connected to water and/or glycerol homeostasis. They can be regarded as a potential drug target, especially in the case of diseases leading to the systemic effects. That is the case with the polycystic ovary syndrome (PCOS), investigated in the current research.

PCOS is defined as a group of symptoms, including: menstrual cycle irregularities, androgen excess and anovulations. It is often accompanied with metabolic abnormalities, like obesity, insulin resistance, hyperinsulinemia, dyslipidemia. The pathogenesis of PCOS remain still controversial, there are three main theories dis-

* Corresponding author.
E-mail address: agata.wawrzkiewicz-jalowiecka@polsl.pl (A. Wawrzkiewicz-Jałowiecka).

http://dx.doi.org/10.1016/j.mehy.2017.03.008
0306-9877/

tinguished: insulin-dependent, LH/FSH and ovarian hypothesis [13,14]. Usually, treatment of polycystic ovary syndrome includes oral contraceptives and metformin, to restore regular menstruation and lower insulin resistance level [15]. As one can see, this kind of therapy is mainly symptomatic, and designing a treatment affecting the cause of PCOS could give better results.

There are clear evidences, that at least three types of aquaporins (AQP7, AQP8, AQP9) exhibit malfunctions, which affect proper follicle growth and quality, in patients with PCOS [7]. Moreover, aquaporins' activity may depend on such factors like e.g. testosterone, estrogens, and glycerol level [16–18] which are commonly altered in PCOS [13,14].

The hypothesis

In this work we would like to raise a fundamental matter: may a genetic defect implying underexpression of aquaporins (at least in granulosa cells and adipocytes) be another important factor in the PCOS pathogenesis?

This idea significantly differs from the commonly used insulin-dependent, LH/FSH and ovarian hypotheses, because it refers to the primary reason of the PCOS on the molecular level. Moreover, due to the ubiquitous presence of aquaporins in human organism and their significant role in many physiological processes, the proposed idea is able to explain the whole diversity of the PCOS symptoms.

To approach the posed problem, we would like to postulate the connections between the functioning and expression of aquaporins, and PCOS symptoms, in order to consider the possibility of application new, promising, AQPs-oriented therapy in women with polycystic ovary syndrome.

At first, we would like to emphasize, that aquaporins −7 and −9 are involved in glucose homeostasis and thus they are already presumed as a drug target in morbid obesity and type 2 diabetes [19,20]. Thus, we postulate that such a therapy could be potentially beneficial for patients with PCOS, considering both the insulin-dependent model of the PCOS pathogenesis, and also frequent occurrence of PCOS-related obesity and insulin resistance.

Secondly, according to the literature reports, the underexpression of AQPs 7–9 was stated in patients with PCOS [7]. We propose a possible mechanism, explaining the impact of alterations of AQPs expression in granulosa cells, on follicle dysfunctions in the PCOS.

Evaluation of the hypothesis

The polycystic ovary syndrome, PCOS, is one of the most common endocrinopathies in women of reproductive age. Common symptoms of PCOS include: menstrual cycle irregularities, mainly oligomenorrhea, signs of androgen excess, such as hirsutism, acne, androgenic alopecia, hyperandrogenemia and ultrasound evidence of polycystic ovaries (at least one ovary containing 12 or more follicles, measuring 2–9 mm or an ovarian volume greater than 10 ml). Metabolic abnormalities are very common in PCOS. Obesity (typically the central obesity), insulin resistance, hyperinsulinemia, dyslipidemia, and other lipid or carbohydrate metabolic disorders are particularly important, as they may develop into metabolic and cardiovascular complications [13,14].

The pathogenesis of PCOS has not been completely clarified. There are 3 main models of pathogenesis PCOS: gonadotropin model, ovarian model and insulin-dependent model, but the role of immune factors and oxidative stress cannot be excluded, as well [21].

As one can see, the question of PCOS pathogenesis evokes still much controversy. It is also believed, that the PCOS has a genetic background and additionally several environmental, ethnic and racial factors play a role [14]. However, we still lack an unambiguous indication, which factors are most significant. In order to approach this problem, we would like to emphasize, that the wide range of disorders, may suggest a systemic origin of that disease, caused, for example, by a set of genetic mutations which, among others, can imply underexpression of AQPs in some prominent locations. Moreover, aquaporins' activity may depend on such factors like e.g. testosterone, estrogens, and glycerol level [16–18], which are commonly altered in the PCOS [13,14].

Role of AQPs in disorders of glycerol homeostasis and its therapeutic potential in PCOS

As the polycystic ovary syndrome is strongly correlated with obesity and insulin resistance [13,14], the possible connections between these disorders and expression of aquaporins are worth noticing.

Aquaporins level has an important impact on adipocyte biology, systemic glucose homeostasis and insulin sensitivity. High hopes are connected with possible aquaglyceroporin-targeted therapy of obesity. Two aquaglyceroporins: AQP7 and AQP9 are involved in adipose tissue metabolism [19,20,22]. Free fatty acids (FFAs) are, usually, the main fuel for skeletal muscles and the heart, but under conditions of increased energy expense, they become almost the sole source of energy. FFAs are produced in adipocytes, – by triacylglycerol hydrolisation to FFAs and glycerol, and, subsequently, released to bloodstream to serve as an energy source. It has been found out, that AQP7 is a glycerol channel, responsible for the glycerol efflux from fat cells, and plays an important role in the mechanism of control and release of glycerol and FFAs into the bloodstream. In research on mice, AQP7 deficiency in adipocytes was associated with adult-onset obesity [23–25]. AQP7-knockout mice had similar body weights to wild-type mice until 12 weeks of age, when, without changing the amount of consumption, their weight gain and fat mass significantly increased [23,24]. AQP7 deficiency resulted in reduced membrane glycerol permeability and threefold reduction of glycerol release [25]. This led to increased glycerol concentration inside adipocytes and increased activity of glycerol-3-phosphate. Then re-esterification of FFAs is favored and it ends with progressive triacyloglycerol accumulation and adipocytes hypertrophy. The research on the association of human AQP7 genetic polymorphism: the A-953G SNP causing AQP7 down-regulation, initially confirmed that it is pathogenic in obesity, as well [26]. Ceperuelo-Mallafré et al. [27] described the association of AQP7 gene expression and obesity in Caucasian subjects. They demonstrated significantly low adipose tissue AQP7 expression levels and low plasma glycerol concentrations in severely obese women. Marrades et al. [28] recruited twelve young men: 6 lean and 6 obese individuals, in order to asses and compare the AQP7 mRNA expression in adipose tissue. The study showed higher adipose AQP7 mRNA expression in lean individuals and lower in the obese ones. In the Chinese in vitro research, the over-expression of AQP7 mRNA was contributed to improve insulin resistance in adipocytes [29].

The regulation of AQP7 expression in fat cells has been reported to be sensitive to fasting–refeeding, insulin, glucocorticoids, tumour necrosis factor (TNF), α adrenoceptor agonists and peroxisome proliferator-activated receptor (PPAR) stimulation [30–32]. The example of drugs activating PPAR receptor are thiazolidinediones, which are used in type 2 diabetes treatment. Thiazolidinediones (TZD) are a type of pill for type 2 diabetes, which increase the levels of adipose fatty acid transporters, such as fatty acid translocase and fatty acid transporter protein, at the transcriptional level. TZD also increases triglycerides in adipocytes, partly through the coordinated induction of AQP7 mRNA and activation of fatty acid transporters and glycerol kinase, suggesting that