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Review: Water channel proteins in the human placenta and fetal membranes

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ABSTRACT

It has been established that the permeability of the human placenta increases with advancing gestation. Indirect evidence has also proposed that aquaporins (AQPs) may be involved in the regulation of placental water flow but the mechanisms are poorly understood.

Five AQPs have been found in the human placenta and fetal membranes [AQP1, 3, 4, 8 and 9]. However, the physiological function(s) and the regulation of these proteins remain unknown.

Emerging evidence has shown that human fetal membrane AQPs may have a role in intramembranous amniotic fluid water regulation and that alterations in their expression are related to polyhydramnios and oligohydramnios.

In addition, we have observed a high expression of AQP3 and AQP9 in the apical membrane of the syncytiotrophoblast. Moreover, AQP9 was found to be increased in preeclamptic placentas, but it could not be related to its functionality for the transport of water and mannitol. However, a significant urea flux was seen.

Since preeclampsia is not known to be associated with an altered water flux to the fetus we propose that AQP9 might not have a key role in water transport in human placenta, but a function in the energy metabolism or the urea uptake and elimination across the placenta. However, the role of AQP9 in human placenta is still speculative and needs further studies.

Insulin, hCG, cAMP and CFTR have been found to be involved in the regulation of the molecular and functional expression of AQPs. Further insights into these mechanisms may clarify how water moves between the mother and the fetus.

1. Introduction

The primary function of the placenta is to promote selective transport of nutrients and waste products between mother and fetus. This function depends on the successful formation and expansion of the human villous syncytiotrophoblast (hST). The hST cell layer, which results from the fusion of the underlying cytotrophoblast cells, is the outermost covering of the placental villi and acts as a physiological barrier between maternal and fetal blood. The hST controls the transcellular movement of water and solutes, helping to maintain normal fetal growth and homeostasis.

Water is an important molecule involved in all biochemical processes in living cells. During pregnancy, fetal water requirements increase markedly due to an exponential growth in fetal weight. Physiological data indicate that both a transcellular and a paracellular pathway are available for transfer across the human placenta, but the morphological correlate of the latter is uncertain [1,2]. In addition, little is known about the molecular mechanisms of these processes.

In many tissues, water channel proteins known as aquaporins (AQPs) have been implicated in transmembrane water transport [3,4]. It is well known that AQPs increase cell plasma membrane water permeability 5–50-fold as compared with membranes in which water moves primarily through the lipid bilayer. In mammals, there are at least 13 AQPs, which show a wide range of distribution in different organs [5]. According to their structural and functional properties, AQPs are divided into three subgroups:

(1) The "classical aquaporins", comprising AQP0, 1, 2, 4, 5, 6 and 8, which are selective only for water. Based on their sequences, AQP6 (also permeable to anions) and AQP8 (also permeable to urea) are included in this subgroup [6,7].
(2) The "aquaglyceroporins", comprising AQP3, 7, 9 and 10, permeable to water, urea and glycerol. AQP9 also facilitates the flux of neutral solutes such as monocarboxylates, purines and pyrimidines [8,9].
(3) The "super-aquaporins", a subgroup recently proposed for two aquaporins: AQP11 and 12, which are localized in the

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cytoplasm and whose permeabilities have not yet been fully determined [10].

Previous research in isolated membrane vesicles has suggested that the movement of water across the hST occurs by a lipid diffusion pathway [11,12]. Nevertheless, we were able to describe the expression of AQP3 and AQP9 in the apical membrane of the hST [13]. Using placental explants in culture, we were able to detect significant uptakes of water, urea and mannitol, sensitive to mercury and phloretin, which indicate the expression of functional AQPs in the normal term placenta [14]. Recently, the importance of the actin cytoskeleton in channel protein regulation has been highlighted and the actin cytoskeleton and its reorganization have been reported to be required for the regulation of both channel activity and intracellular trafficking [15]. Thus, a possible explanation for the discrepancy in the functional experiments is that, in those performed in isolated vesicles, some of the components of the cytoskeleton which may be important for the functionality of AQPs may be excluded.

Many authors have reported the expression of AQPs in the human placenta and fetal membranes (Table 1). Mann and co-workers found expression of AQP1 and AQP3 in fetal membranes and suggested that AQPs may contribute to amniotic fluid volume regulation. They also localized AQP1 in the capillary endothelium of placental vessels [16]. In addition, Wang and co-workers reported the expression of AQP8 and AQP9 in chorioamniotic membranes [17,18], whereas De Falco and co-workers described the expression of AQP4 in the hST, and its downregulation throughout pregnancy [19].

2. Role of AQPs in the human placenta and fetal membranes

AQPs are not only involved in several physiological processes but also in multiple and diverse clinical dysfunctions [4].

Under normal conditions, water flow progressively increases throughout gestation; near term, up to 400 mL per day are transferred from the amniotic cavity across the fetal membranes into the fetal circulation [20]. Because of the osmotic pressure difference between amniotic fluid (255 mOsm/kg) and fetal blood (280 mOsm/kg), an osmotic gradient drives transport of fluid and solutes from the amniotic compartment into the fetal blood [21]. It has also been reported that the permeability of the human amnion *in vitro* is 1.5×10^{-4} cm $\times$ s^{-1} [22]. The regulation of placental water transfer and intramembranous resorption are poorly understood; however, both phenomena support the hypothesis that AQP water channels may be fundamental to the regulation of fetal water flow [23].

Mann and co-workers explored the association between polyhydramnios and AQP1 and found an increase in AQP1 expression particularly in the amnion (33-fold) in pregnancies complicated by idiopathic polyhydramnios [24]. Thus, they postulated that this upregulation is a compensatory response to polyhydramnios. Moreover, Zhu et al. found that the expression of AQP8 in the amnion and of AQP9 in the amnion and the chorion were significantly increased in idiopathic polyhydramnios, but that their expression in the placenta was significantly decreased [25]. These authors suggested that when idiopathic polyhydramnios occurs, some modulation factors may be inducing the changes in expression of AQP8 and AQP9. Consequently, these changes may increase the intramembranous absorption and decrease the maternal-to-fetal water flow to maintain amniotic fluid homeostasis. On the other hand, in pregnancies complicated with oligohydramnios, a decrease in AQP1 expression in the amnion but no significant changes in the chorion and in the placenta have been observed [26]. Decreases in AQP3 in the amnion and in the chorion as well as a significant increase in the placenta have also been found [26]. However, to date, no study has examined their functional significance in human abnormal amniotic fluid volume and only indirect evidence suggests that these proteins may be involved in the regulation of placental water flow.

In trophoblast tissue, we have previously reported the expression of AQP3 and AQP9 [13] and postulated that these aquaglyceroporins could participate not only in the water transport between mother and fetus, but also in the rapid movement of solutes across cell membranes, with minimal osmotic perturbation. In subsequent experiments, in preeclamptic placentas, we observed an increase in AQP9 expression by Western blot and a different cellular distribution of AQP9 protein by immunohistochemistry (Fig. 1). AQP9 was localized not only in the apical membrane but also in the basal membrane and in the cytoplasm of preeclamptic hST cells [14]. We assumed the increase in AQP9 to correlate with an increase in water flux. In contrast, the uptakes of water and mannitol in preeclamptic placental explants decreased when compared to those observed in normal explants and were not sensitive to $HgCl_2$ (Table 2). Since mannitol flux sensitive to $HgCl_2$ is specific for AQP9, these results may suggest a lack of functionality of AQP9 for water and mannitol in preeclampsia. Interestingly, urea uptake sensitive to phloretin and mercury increased 35% in preeclamptic explants (Table 2). These data indicate that water and solute permeabilities of AQP9 are modified under pathological conditions. Since preeclampsia is not known to be associated with an altered water flux to the fetus, our results led us to hypothesize that, although AQP3 may play a role in transcellular water transport across the hST, the role of AQP9 exclusively in water homeostasis should be revised. AQP9 is of special interest because, in addition to being permeable to water, it is permeable to neutral solutes [8] suggesting that this channel may also be involved in metabolite diffusion and may therefore have a role in energy metabolism.

In hepatocytes, the presence of AQP9 suggests that this pore could function as a glycerol channel, where glycerol participates in the gluconeogenesis during fasting periods, or also facilitate the diffusion of urea [27]. Indeed, a huge increase in AQP9 expression was observed after a 4-day fasting diet whereas a decrease in AQP9 to control levels was observed after refeeding [27].

It has also been postulated that AQP9 could be involved in brain energy metabolism as a metabolite channel [28]. Thus, AQP9 may facilitate the diffusion of glycerol and monocarboxylates, which serve as energy substrates for neurons [28]. In addition, lactate permeability increases in acidic conditions [8]. Consequently, during brain ischemia, lactic acidosis may increase the permeability of AQP9 to lactate and therefore enable the uptake of excess lactate by astrocytes. In this way, AQP9 could favor lactate and glycerol clearance from the extracellular space during ischemia. At later time points after reperfusion, AQP9 may facilitate lactate movement between astrocytes and neurons for use as an energy

Table 1
Localization of AQPs in the human placenta and fetal membranes.

Aquaporin	Location	References
AQP1	Chorion	Mann et al. [16]; Zhu et al. [26]
	Amnion	Mann et al. [16]; Zhu et al. [26]
	Placental vessels	Mann et al. [16]; Zhu et al. [26]
AQP3	Chorion	Wang et al. [33]; Zhu et al. [26]
	Amnion	Wang et al. [33]; Zhu et al. [26]
	Trophoblast	Damiano et al. [13]; Wang et al. [33]; Zhu et al. [26]
AQP4	Trophoblast	De Falco et al. [19]
AQP8	Chorion	Wang et al. [17]
	Amnion	Wang et al. [17]
	Trophoblast	Wang et al. [17]
AQP9	Chorion	Wang et al. [18]
	Amnion	Wang et al. [18]
	Trophoblast	Damiano et al. [13]; Wang et al. [18]

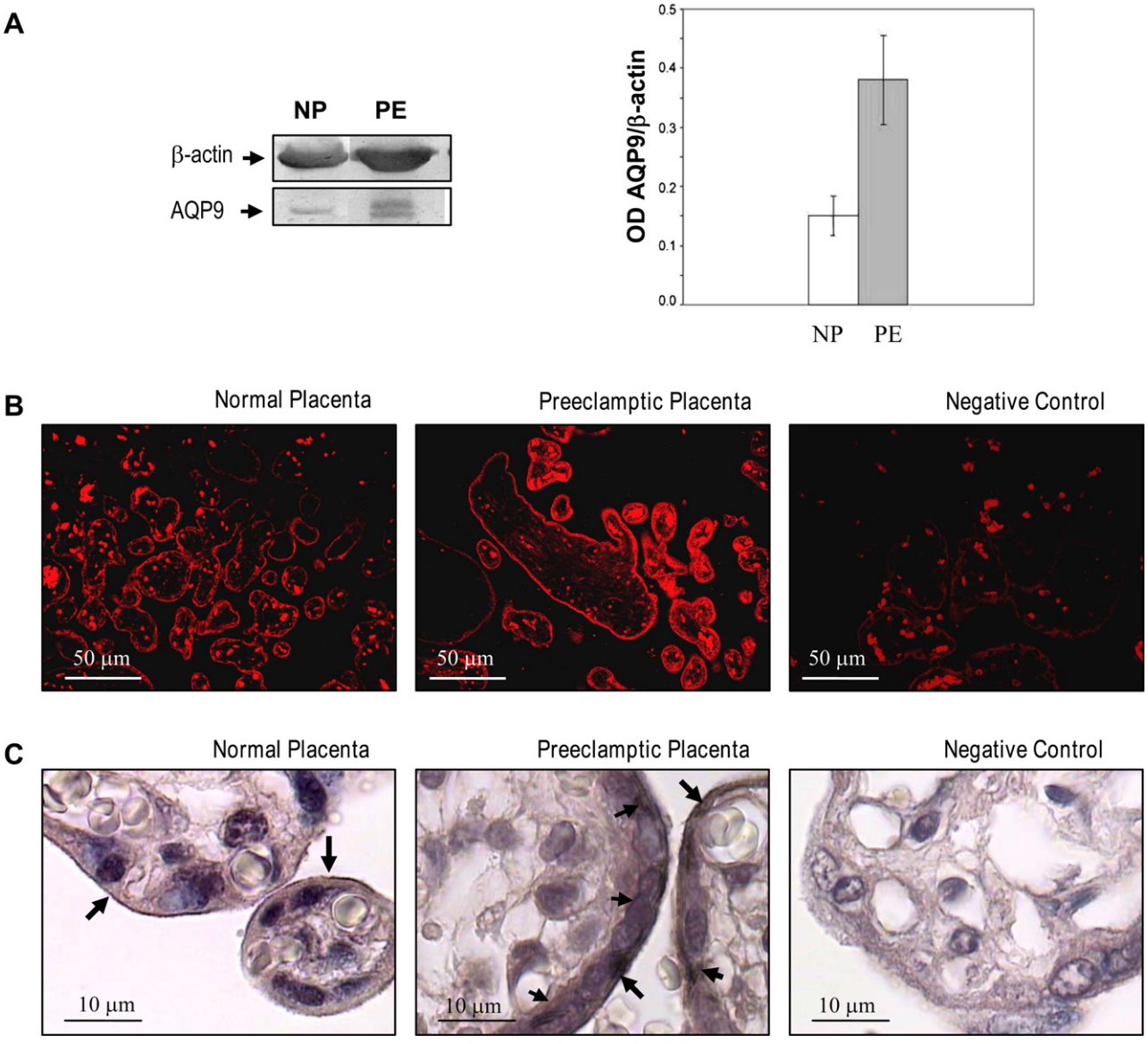

Fig. 1. AQP9 protein expression in hST from normal and preeclamptic placentas A) Semiquantitative immunoblotting analysis of AQP9 abundance in hST. A representative immunoblot shows that AQP9 protein level expression was significantly higher in preeclamptic (PE) than in normal placenta (PN). Densitometry of immunoblots containing AQP9 protein level expression was performed, and after normalization for β-actin, the values are plotted as AQP9/β-actin relative ratio. Each plotted value corresponds to the mean ± SEM obtained in five placentas (*$P < 0.05$). B) Immunofluorescence showed AQP9 normal expression in apical membrane of hST from normal placentas while in preeclamptic placentas, an increase in AQP9 signal was observed. Magnification: ×200. C) Immunoperoxidase staining confirmed AQP9 specific labeling in the apical membrane of hST from normal placenta. In preeclamptic placenta AQP9 immunolabeling was not only in the apical membrane but also in the basal membrane and in the cytoplasm of hST. Magnification: ×1000. Negative controls were performed by omitting primary antibody and replaced by a non-immune rabbit serum. Data reproduced from [14,43], with permission, where further experimental details may be found.

substrate after ischemic insults [28,29]. However, these hypotheses concerning the function of brain AQP9 are still speculative.

Analogously, we may hypothesize that in placental pathologies, such as preeclampsia, characterized by a shallow implantation which leads to a relatively hypoxic maternal–fetal interface, AQP9 might be involved in energy homeostasis.

Finally, we cannot exclude a possible role for AQP9 channels in the diffusion of urea. We have previously reported the expression of a urea transporter type A (UT-A) in the human placenta [14]. AQP9 could complement UT-A function, participating in urea uptake and elimination across the placenta.

In addition, AQPs have been associated with changes in cellular volume during apoptosis [30]. Apoptosis has been reported to increase progressively throughout pregnancy and is suggested to play a role in the differentiation, syncytial fusion and degeneration of villous trophoblasts [31]. Increased apoptosis, as a consequence of an inadequate trophoblast invasion, has also been found in placentas from pregnancies complicated by preeclampsia [32].

So far, whether or not AQP3 and AQP9 play a direct role either in the pathogenesis or in the adaptive response of preeclampsia is still uncertain and thus needs further studies.

3. Regulation of AQPs in the human placenta and fetal membranes

Little is known about the mechanisms that control and regulate AQPs in the human placenta and fetal membranes. Several studies suggest that AQP3 and AQP8 expression in human amniotic

Table 2
Water, urea and mannitol uptakes in normal and preeclamptic placental explants.

	Normal placental explants	Preeclamptic placental explants
Water uptake, pmol g^{-1} min^{-1}		
Control	76 ± 6	47 ± 10
+ $HgCl_2$ 0.3 mM	48 ± 7	36 ± 12
Mannitol uptake, pmol g^{-1} min^{-1}		
Control	14.6 ± 0.3	5.5 ± 0.6
+ $HgCl_2$ 0.3 mM	7.8 ± 0.8	6.0 ± 2.3
Urea uptake, pmol g^{-1} min^{-1}		
Control	15.2 ± 0.6	20.5 ± 0.9
+ $HgCl_2$ 0.3 mM	8.8 ± 0.4	11.1 ± 0.8
+0.5 mM phoretin	10.6 ± 0.3	10.4 ± 0.6

Water uptake: In normal placental explants, water uptake was significantly inhibited by 0.3 mM $HgCl_2$ ($P < 0.01$). In preeclamptic explants, water uptake was smaller than in normal ones ($P < 0.01$) and it was not sensitive to $HgCl_2$. *Mannitol uptake*: In normal placentas, mannitol uptake was inhibited by $HgCl_2$ ($P < 0.001$). However, in preeclamptic explants, mannitol uptake decreased compared to normal explants ($P < 0.001$) and it was not sensitive to $HgCl_2$. *Urea uptake*: In normal placental explants urea uptake was inhibited either by 0.3 mM $HgCl_2$ ($P < 0.001$) or by 0.5 mM phloretin ($P < 0.001$). In preeclamptic explants, urea uptake increased 35% compared to normal explants ($P < 0.001$) and was inhibited by 0.3 mM $HgCl_2$ ($P < 0.001$) and by 0.5 mM phloretin ($P < 0.001$). Data reproduced from [14], with permission, where further experimental details may be found.

epithelial cells are stimulated by cAMP [33,34]. Furthermore, Belkacemi and co-workers have recently established that, in trophoblast-like cells, AQP1 gene expression is upregulated by vasopressin and cAMP agonists [35]. These authors also demonstrated that a cAMP-dependent pathway is responsible for the vasopressin effect on AQP1 expression. These effects may be noteworthy, as vasopressin levels are increased in the amniotic fluid of fetuses with oligohydramnios [36], where it has been proposed that AQP1 may be regulating the amniotic fluid volume. On the other hand, we have studied water and neutral solute fluxes in trophoblast tissue and detected a functional AQP3 and AQP9 in the normal term placenta [14]. However, up to now, only the regulation of AQP9 was studied in human placenta.

We have investigated the effect of placental hormones on transcellular water flux and provided evidence that human chorionic gonadotropin (hCG) may have a stimulatory effect on the molecular expression and functionality of AQP9 via cAMP pathways [37]. In normal placental explants treated with different concentrations of recombinant hCG or 8-Br-cAMP, a potent analogue of cAMP, AQP9 protein expression increased significantly compared to the non-treated explants. This effect on AQP9 expression was dependent on hCG and cAMP concentrations and AQP9 cellular distribution was similar to that observed in preeclamptic placentas. In addition, in normal placental explants, the increase in the expression of AQP9 protein was related to an increase of 1.6-fold in transcellular water flux. However, despite the high levels of hCG observed in preeclamptic pregnancies and the increase in placental AQP9 expression, water uptake decreased, probably due to other factors which may be altering AQP functionality.

In this regard, we have tested the interaction between cystic fibrosis transmembrane conductance regulator (CFTR) and AQP9. Increasing evidence indicates that CFTR is able to interact with various membrane proteins by regulating their transport activity as well as by functioning as a cAMP-regulated chloride channel [38]. Thus, we have hypothesized that water transport mediated by AQPs may be regulated by CFTR. CFTR, AQP9 and AQP3 are localized on the apical membrane of the hST and are believed to play a role in electrolyte and water transport from the mother to the fetus [13,39].

We showed that CFTR protein expression decreased dramatically (3.8-fold) in the hST from preeclamptic placentas [40]. In addition, we studied water uptake in normal and preeclamptic placental explants treated with diphenylamine- 2-carboxylate (DPC), 4,4′-diisothiocyanatostilbene-2,2′-disulfonic acid (DIDs) (inhibitors of chloride channels) and glibenclamide (an open-channel blocker of CFTR). Water uptake was significantly reduced by all the inhibitors of CFTR [DIDs and DPC ∼35%, glibenclamide ∼50% ($P < 0.05$)]. In contrast, water uptake in explants from preeclamptic placentas showed a decrease of ∼51% ($P < 0.05$) compared to normal placentas. Interestingly, water uptake was not modified by the inhibitors tested, possibly due to the reduced expression of CFTR in preeclampsia. There was no evidence that CFTR could function as a water channel per se, so we speculated that the CFTR protein was required to preserve the normal functionality of AQPs. Our finding is consistent with a synergistic effect of these proteins. Although the inductor mechanisms that cause a decrease in the levels of CFTR protein in preeclamptic placentas are not yet clear, we have suggested that this decrease may affect placental water transport mediated by AQPs.

We also analyzed the lipid membrane composition of the hST cells. Studies on human placental hST have demonstrated that fluidity of the membrane phospholipids plays an essential role in modulating membrane transport processes [41]. It is well known that factors like cholesterol and sphingomyelin content, fatty acyl chain length and degree of unsaturation in the membrane are major determinants of fluidity [42]. Moreover, Illsley and co-workers reported that throughout gestation the composition, structure and functions of hST membrane lipid bilayers are modified in order to meet the changing metabolic needs of the growing fetus [43].

In recent studies (unpublished), we have found that sphingomyelin increased 1.5-fold in apical membranes of preeclamptic hST compared to normal hST and that the amount of cholesterol did not change ($n = 25$; $P < 0.05$). In electron paramagnetic resonance (EPR) experiments, we confirmed that the apical membrane fluidity decreased significantly in preeclamptic placentas. Hence, we speculate that alterations in the lipid membrane composition of hST may also alter the transcellular water transport.

Furthermore, we have investigated the effect of insulin on AQP9. In accordance with earlier reports in brain and liver [28,44], the increase in insulin concentration may reduce the levels of both AQP9 mRNA and protein, possibly due to a negative insulin response element in the promoter region of AQP9. We have observed that in normal placental explants insulin treatment downregulates AQP9 expression [45] but not AQP3. However, water uptake was similar in both treated and non-treated explants, suggesting that the expression of AQP9 is not essential for water transfer across the human placenta.

4. Conclusion

After the first report of AQP3 and AQP9 in the human placenta, a number of AQPs have been found to be expressed in trophoblast and in fetal membranes. Fetal water requirements are satisfied primarily via transplacental transfer from the maternal circulation, suggesting a need for increased placental water flux with advancing gestation. AQP1, AQP3, AQP8 and AQP9 may be involved in regulation of the amniotic fluid volume. Alterations in the expression of AQPs in human fetal membranes may be associated with idiopathic polyhydramnios or oligohydramnios.

AQP3 and AQP9 are highly expressed in the normal hST. AQP9 is upregulated in the preeclamptic hST but this could not be related to an increase in water flux. Preeclampsia is not known to be associated with an altered water flux to the fetus, so the increase in expression of AQP9 may be a response due to an additional role of this protein. However, hypotheses concerning the function of placental AQPs are still speculative.

Insulin, hCG and cAMP have been found to be involved in the molecular and functional expression of AQP9. CFTR has also been involved in the modulation of water transport in the human placenta.

However, to determine the modulation factors by which AQPs can be regulated in the human placenta requires further work. Finally, the exact roles of these AQPs and the relationship between changes in AQP expression and placental pathologies need more study.

Conflict of interest

The author declares that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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