Regulation of Iodide Uptake in Placental Primary Cultures

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Abstract

Background: Maintenance of adequate iodide supply to the developing fetus is dependent not only on maternal dietary iodine intake but also on placental iodide transport. The objective of this study was to examine the effects of different pregnancy-associated hormones on the uptake of radioiodide by the placenta and to determine if iodide transporter expression is affected by hormone incubation. **Methods:** Primary cultures of placental trophoblast cells were established from placentas obtained at term from pre-labor caesarean sections. They were pre-incubated with 17β-estradiol, prolactin, oxytocin, human chorionic gonadotropin (hCG) and progesterone either singly or in combination over 12 h with ^{125}I uptake being measured after 6 h. RNA was isolated from placental trophoblasts and real-time RT-PCR performed using sodium iodide symporter (NIS) and pendrin (PDS) probes. **Results:** Significant dose response increments in ^{125}I uptake by trophoblast cells (p < 0.01) were observed following incubation with hCG (60% increase), oxytocin (45% increase) and prolactin (32% increase). Although progesterone (50–200 ng/ml) and 17β-estradiol (1,000–15,000 pg/ml) alone produced no significant differences in uptake, they facilitated increased uptake when combined with prolactin or oxytocin, with a combination of all four hormones producing the greatest increase (82%). Increased ^{125}I uptake was accompanied by corresponding increments in NIS mRNA (ratio 1.52) compared to untreated control cells. No significantly increased expression levels of PDS were observed. **Conclusions:** Pregnancy-associated hormones, particularly oxytocin and hCG, have a role in promoting placental iodide uptake which may protect the fetus against iodine deficiency.

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Introduction

The supply of iodide for hormone synthesis by the fetal thyroid is dependent not only on maternal iodine intake and placental deiodination of thyroxine, but also on placental capacity to accumulate iodide and transport it to the fetal compartment [1–3]. The demonstration of both the sodium iodide symporter (NIS) and pendrin (PDS) within the placental trophoblasts [4, 5] has suggested a mechanism whereby iodide is taken up by NIS and then released to the fetal compartment by PDS. More recent reports have demonstrated that NIS expression was pres-

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ent in early pregnancy and remained relatively constant throughout gestation [6–8]. A postulated mechanism for iodide transport was tested in the BeWo cell line [9] and placental iodide uptake was found to be similar to thyroidal transport both in terms of the protein responsible for uptake (NIS) and the inhibitors of such uptake [10–12]. The deiodinases D3 and, to a lesser extent, D2 have been demonstrated in placenta and have a role in iodine supply to the fetus [13]. Upregulation of NIS in both fetal and placental tissue has also been found in rats on a low iodine diet [14], suggesting the existence of a compensatory system for inadequate iodine intake to ensure sufficient iodide for normal fetal development. Previous studies by our group have shown similar levels of iodide uptake in placenta to that of thyroid and have identified a previously unreported capacity of the placenta to store iodine [15].

Human chorionic gonadotropin (hCG) has been shown to stimulate the accumulation of anionic iodide and increase the expression of NIS mRNA and protein in both the Jar [16] and BeWo choriocarcinoma [9, 17] cell lines. Other pregnancy-related hormones such as oxytocin [18], prolactin [19] and 17β-estradiol [20] have been shown to increase iodide uptake in both mice and human mammary cancer cells.

The aims of this study were to determine the effects of these pregnancy-related hormones, both individually and in combination, on iodide accumulation and iodide transporter expression levels within placental primary cultures prepared from fresh tissues collected at term rather than in cell lines.

Materials and Methods

Tissue Collection

Placentas (n = 9) were obtained from a random group of euthyroid women undergoing elective pre-labor caesarean section at term. All patients were having their first caesarean section. Ethical approval was granted by the Ethics Committee, National Maternity Hospital, Dublin, Ireland. Sections were carried out after 38–40 weeks of gestation and were elective with no associated pathology. The Irish pregnant population from which placental samples were obtained would be classified as borderline iodine deficient (median urinary iodine 84 μg/l) [21].

Establishment of Placental Primary Culture

Placental primary culture of human cytotrophoblasts was carried out according to the method of Petroff et al. [22]. Placentas were obtained from women undergoing elective pre-labor caesarean section at term gestation (>37 weeks). Tissue was physically and enzymatically dispersed. Cells were fractionated on a discontinuous Percoll gradient and the trophoblast cell population was purified by MACS® immunomagnetic separation (Miltenyi Biotec, Auburn, Calif., USA). This separation is based on the fact that HLA class 1 molecule is expressed in extra-villous and syncytiotrophoblast cells but not on cytotrophoblasts. The HLA-labeled magnetic beads bind to the column and are thereby removed, purifying the population. Cells were seeded at 2×10^5 cells/cm^2 in appropriate culture vessels. The cytotrophoblast culture medium was Iscove's Modified Dulbecco's Medium (IMDM) containing 10% heat-inactivated FBS, 2 mM L-glutamine and 1× penicillin/streptomycin/amphotericin B (100× solution). Cells were allowed to attach and grown for at least 48 h following separation.

Radioiodide Uptake

The ability of cells to accumulate iodide was determined according to the method described by Ajjan et al. [23]. Cells were incubated in the presence of anionic iodide I$^-$ (^{125}I) and optimum incubation times were established experimentally (peak uptake of ^{125}I occurred between 6 and 9 h; results not shown). Radioiodide with an activity of 10,000 cpm was prepared in serum-free media and the ^{125}I was added to the cells. Approximately 1 cm^3 portions of each tissue type were washed in buffered Hanks' balanced salt solution (HBSS) and finally rinsed with serum-free media before incubation. Radioiodide with an activity of 40,000 cpm was prepared in 2 ml serum-free media and the ^{125}I was added to the cells. To account for variation in tissue composition, results were expressed in cpm/μg DNA with DNA content being measured using a Qiagen DNA extraction kit. Pre-incubation with levels of the various pregnancy-related hormones [24–28] shown in table 1 was performed over 12 h. These values were selected as being in the range of representative values likely to be encountered in late pregnancy (17β-estradiol 15,000 pg/ml; progesterone 100 ng/ml; prolactin 100–200 μIU/ml; hCG <100 mIU/ml; oxytocin <10 IU/ml) [24, 25]. Results of ^{125}I uptake are shown in figures 1–5 as the changes in percentage of uptake compared to controls. In addition to varying concentrations of the individual hormones, cells were incubated with combination hormone preparations consisting of mixtures of the three hormone preparations (low, intermediate and high).

Figures 1–5 also show the effect on the uptake of incubating with potassium perchlorate (100 μM) which was included in incubation mixtures for both individual hormones and combinations (low, intermediate and high). Maximum perchlorate-independent ^{125}I uptake (control vs. perchlorate) termed 'net iodide uptake' is described in both the text and figure legends.

Concentrations of hormones used are shown in table 1 [24–28]. Subsequent iodide uptake was measured after 6 h of incubation. Uptakes were performed in the presence and absence of potassium perchlorate (100 μM), a known inhibitor of NIS. Following ^{125}I incubation, cells were rinsed twice with ice-cold PBS and accumulated ^{125}I was determined by lysing the cells in NaOH and then reading the radioactivity on a γ-counter. Results [counts per minute (cpm)] were expressed as a percentage of control (hormone-free) values.

RNA Extraction and Real-Time PCR

Total RNA was extracted from placental trophoblasts with the Qiagen RNA isolation kit (Abgene, Surrey, UK). RNA concentration was determined by OD$_{260}$ and quality checked by electrophoresis on 1% agarose. One microgram of total RNA was reverse transcribed with Superscript III Reverse Transcriptase using oligo-

Fig. 1. Effect of 17β-estradiol (**a**), progesterone (**b**) and 17β-estradiol + progesterone combination (**c**) on ^{125}I uptake and iodide transporter (NIS and PDS) expression in placental trophoblast primary culture as compared with untreated control cells. Potassium perchlorate- (100 μM) treated cells are included as a negative control. Real-time quantitative PCR of NIS and PDS is displayed linearly as a ratio comparing treated cells to untreated controls. E2 = 17β-Estradiol.
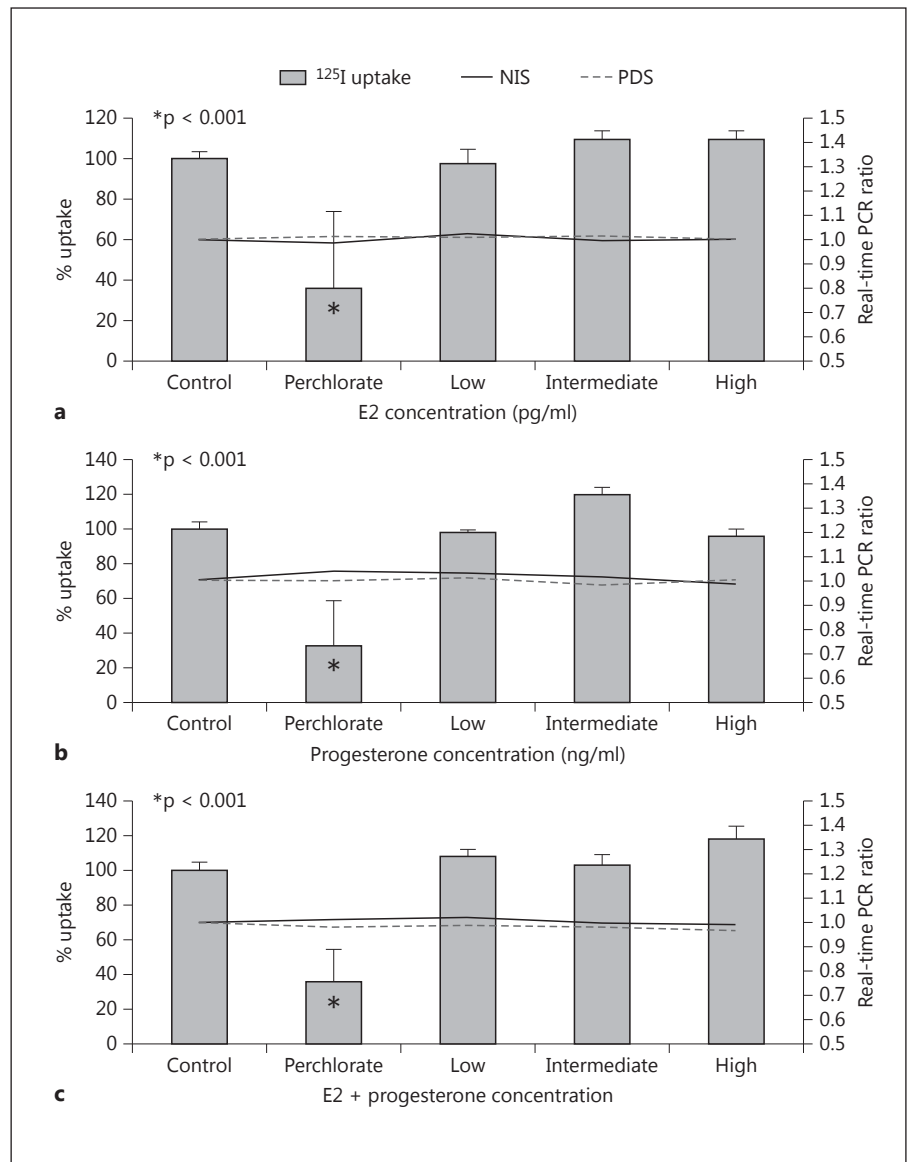
Table 1. Final concentrations of hormones incubated with trophoblast cells to determine their effect on iodide uptake and iodide transporter expression

Hormones	Concentrations			Ref.
	Low	Intermediate	High	
17β-Estradiol, pg/ml	1,000	7,000	15,000	27
Progesterone, ng/ml	50	100	200	27
Prolactin, μIU/ml	100	200	300	28
hCG, mIU/ml	10,000	50,000	300,000	25
Oxytocin, IU/ml	10	100	1,000	26

Hormone concentrations were selected (low, medium and high) to correspond with concentrations during different stages of pregnancy [24–28]. Combinations of hormones were comprised of all low, intermediate or high doses, respectively.

Fig. 2. Effect of prolactin (**a**) (maximum net iodide uptake 22%) and 17β-estradiol + progesterone + prolactin combination (**b**) (maximum net iodide uptake 38%) on ^{125}I uptake and iodide transporter (NIS and PDS) expression in placental trophoblast primary culture as compared with untreated control cells. Potassium perchlorate- (100 μM) treated cells are included as a negative control. Real-time quantitative PCR of NIS and PDS is displayed linearly as a ratio comparing treated cells to untreated controls. E2 = 17β-Estradiol.
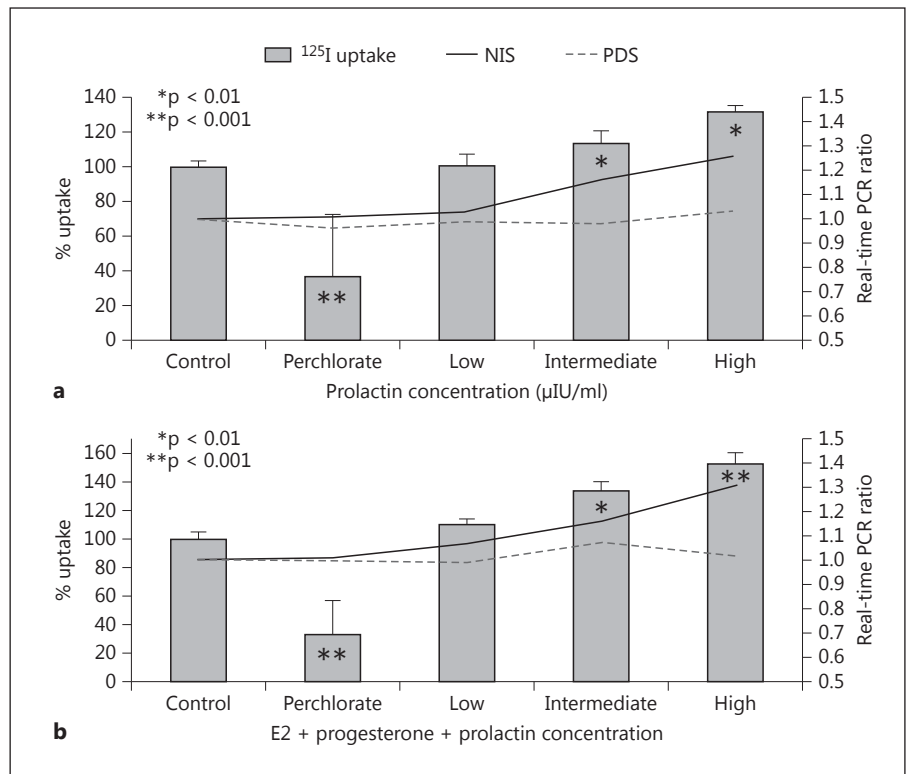

Fig. 3. Effect of hCG (βCG Sigma Aldrich 93659) on ^{125}I uptake (maximum net iodide uptake 26%) and iodide transporter (NIS and PDS) expression in placental trophoblast primary culture as compared with untreated control cells. Potassium perchlorate- (100 μM) treated cells are included as a negative control. Real-time quantitative PCR of NIS and PDS is displayed linearly as a ratio comparing treated cells to untreated controls.
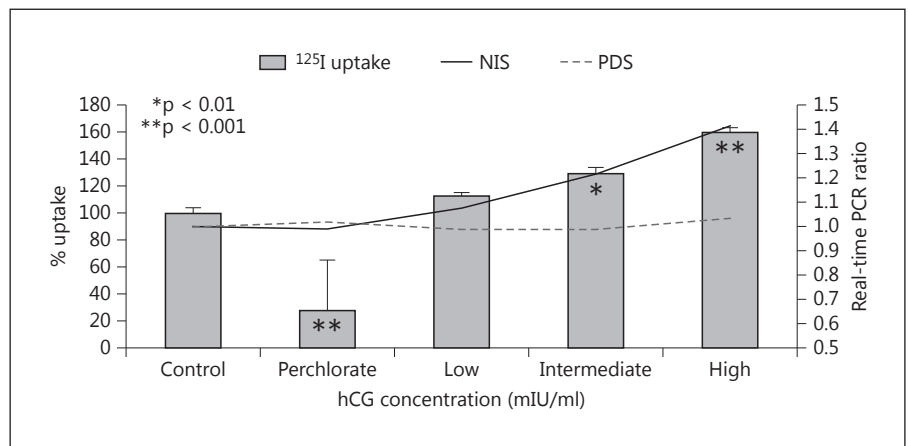
dT primers in a reaction volume of 20 μl. Four microliters of the cDNA product was used in the PCR reaction with 2.5 mM $MgCl_2$, 0.2 mM mixed dNTP, 0.15 μM specific primers and 0.5 U Platinum *Taq* DNA Polymerase (Invitrogen) in a total volume of 20 μl. Thirty-four PCR cycles with denaturation at 94°C (1 min), annealing at 60°C (30 s) and extension at 70°C (30 s) were carried out in a GeneAmp PCR System 9700. Primer pairs for NIS and PDS were designed using published cDNA sequences [29, 30]. The ABI Prism 7700 sequence detection system was used for TaqMan real-time PCR. To validate the real-time RT-PCR method, standard curves for NIS and 18S ribosomal RNA were constructed from PCR products that were serially diluted in nuclease-free water. The 18S RNA for each sample was divided by the target mRNA to de-

termine a normalized ratio. Results were expressed as a ratio of the NIS and PDS expression levels in the incubated cells versus untreated controls.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism software (version 4.0; GraphPad Software Inc., San Diego, Calif., USA). Significant differences in mean percentage of ^{125}I uptake or NIS and PDS ratios between the means of incubated cells and the untreated control group were compared using ANOVA with Bonferroni's post hoc test. Results are expressed as percentage of uptake ± SD and p < 0.05 was considered significant.

Fig. 4. Effect of oxytocin (**a**) (maximum net iodide uptake 33%) and 17β-estradiol + progesterone + oxytocin combination (**b**) (maximum net iodide uptake 40%) on ^{125}I uptake and iodide transporter (NIS and PDS) expression in placental trophoblast primary culture as compared with untreated control cells. Potassium perchlorate- (100 μM) treated cells are included as a negative control. Real-time quantitative PCR of NIS and PDS is displayed linearly as a ratio comparing treated cells to untreated controls. E2 = 17β-Estradiol.
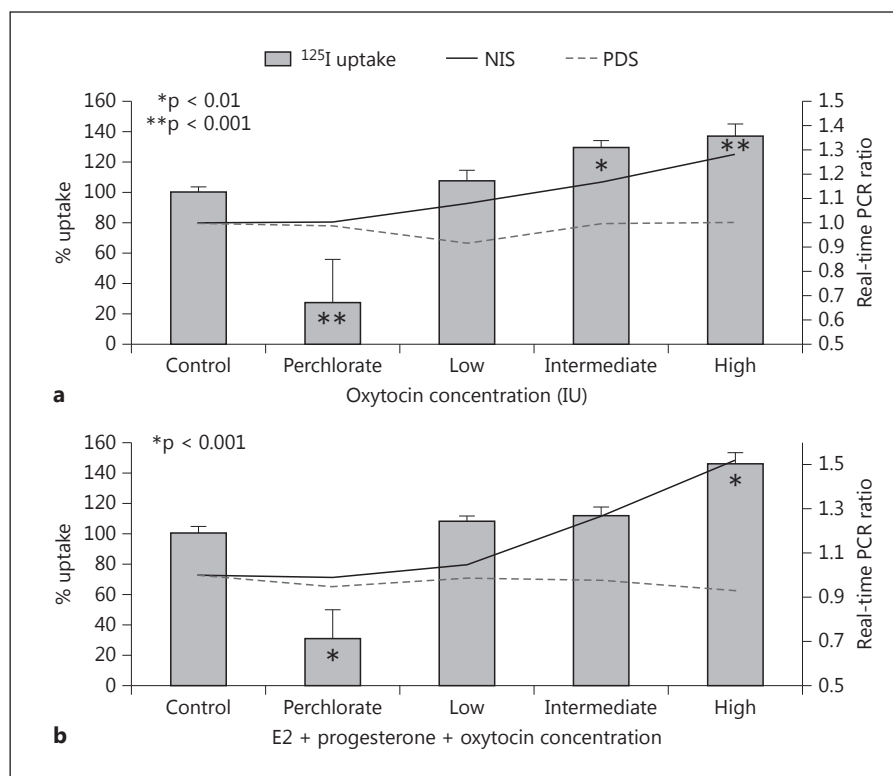

Fig. 5. Effect of 17β-estradiol + progesterone + prolactin + oxytocin combination on ^{125}I uptake (maximum net iodide uptake 83%) and iodide transporter (NIS and PDS) expression in placental trophoblast primary culture as compared with untreated control cells. Potassium perchlorate- (100 μM) treated cells are included as a negative control. Real-time quantitative PCR of NIS and PDS is displayed linearly as a ratio comparing treated cells to untreated controls. E2 = 17β-Estradiol.

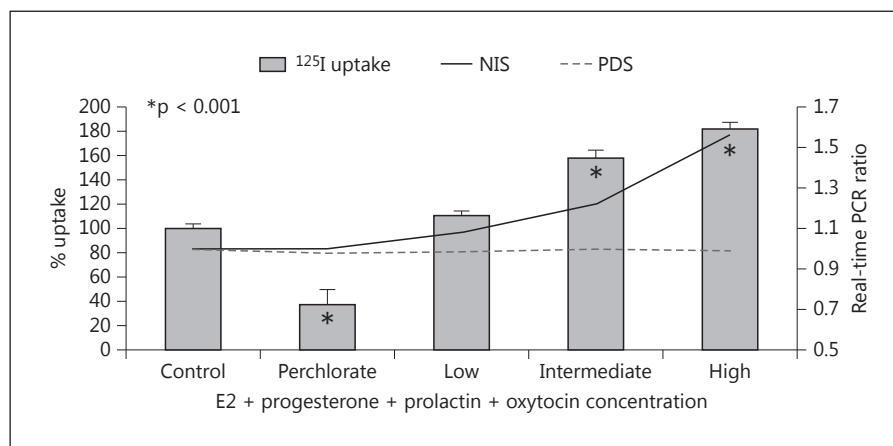## Results

Figures 1–5 show results of ^{125}I uptake in primary cultures of human cytotrophoblasts in the presence or absence of individual hormones or combinations of hormones at concentrations shown in table 1. At every hormone incubation examined, potassium perchlorate had a significant (p < 0.001) effect on iodide uptake, with an uptake that decreased to between 28 and 38% of that of control untreated trophoblast cells. These decreases in uptake were not accompanied by changes in either NIS or PDS expression.

17β-Estradiol and Progesterone Effect on Radioiodide Uptake and Iodide Transporter Expression

The effects of 17β-estradiol, progesterone and 17β-estradiol + progesterone combination incubation on ^{125}I uptake in trophoblast cells are shown in figure 1. Neither 17β-estradiol nor progesterone individually or in combination had any significant effect on ^{125}I uptake. Incubation with these hormones had no significant effect on the levels of expression of either NIS or PDS as measured by real-time PCR.

Prolactin Effect on Radioiodide Uptake and Iodide Transporter Expression

Figure 2a shows the effect of prolactin incubation on ^{125}I uptake in trophoblast cells. Varying concentrations of prolactin from a concentration of 100–300 µIU/ml increased uptake by up to 32%. Maximum net iodide uptake was 22%. Significant increases in uptake were observed following incubation with 200 and 300 µIU/ml, respectively (p < 0.01). There were also corresponding increases in the levels of expression of NIS after prolactin incubation compared with untreated trophoblast cells [1.03, 1.16 and 1.26 after incubation with 100, 200 (p < 0.01), and 300 µIU/ml prolactin (p < 0.001), respectively]. There were no increases in the level of PDS expression after incubation with prolactin. Figure 2b shows that the increase in uptake observed after incubation with prolactin alone was amplified when this hormone was combined with progesterone and 17β-estradiol, despite the fact that neither of these hormones, alone and in combination, had any effect on ^{125}I uptake or NIS expression. These three hormones in combination significantly increased ^{125}I uptake by up to 52% at the highest concentrations of the three hormones (p < 0.001). Maximum net iodide uptake was 38%. NIS expression levels were also significantly increased in the trophoblast population compared with untreated cells (1.31; p < 0.001) after incubation with the highest concentrations of the three hormones.

hCG Effect on Radioiodide Uptake and Iodide Transporter Expression

hCG showed the greatest increase in uptake of radioiodide in trophoblast cells of all individual hormones as shown in figure 3. Uptake of iodide by hCG-incubated trophoblasts exhibited saturable uptake of radioiodide that increased steadily when hCG concentrations were increased from 10,000 mIU/ml (30%; p < 0.01) to 50,000 mIU/ml (60%; p < 0.001) and further increased at a concentration of 300,000 mIU/ml (p < 0.001). Maximum net iodide uptake was 26%. hCG incubation also significantly increased NIS expression levels in the trophoblast cells as compared with untreated cells [1.08, 1.22 and 1.42 after incubation with 10,000 (p < 0.05), 50,000 (p < 0.05) and 300,000 mIU/ml hCG (p < 0.01), respectively]. No changes in PDS expression levels were observed after hCG incubation.

Oxytocin Effect on Radioiodide Uptake and Iodide Transporter Expression

Figure 4a shows the effect of oxytocin incubation on iodide uptake in trophoblast cells. By varying concentrations of oxytocin from 10 to 1,000 IU/ml, uptake increased in a dose-dependent manner by 5–40% with a spike of 45% at 200 IU/ml (not shown). Maximum net iodide uptake was 33%. Further increases in oxytocin concentration produced small decreases in uptake, although these remained significantly elevated (intermediate 13%; p < 0.01 and high 30%; p < 0.001) compared to control untreated cells. As was observed with hCG and prolactin incubation, oxytocin incubation also increased NIS expression levels (1.08, 1.17 and 1.28) in a dose-dependent manner (100 IU/ml; p < 0.05 and 1,000 IU/ml; p < 0.01) within the incubated trophoblast population but had no effect on PDS expression levels.

As with prolactin, combining the incubation of oxytocin with the 17β-estradiol + progesterone combination induced a greater increase in ^{125}I uptake compared with oxytocin alone, despite the fact that neither progesterone nor 17β-estradiol alone or in combination altered radioiodide uptake. As shown in figure 4b, these three hormones in combination significantly increased uptake by up to 46% at the highest concentrations (p < 0001), which was similar to the maximum effect of 45% produced by the 200 IU/ml oxytocin when tested alone. Maximum net iodide uptake was 40%. NIS expression levels in cells treated with the three hormones were significantly increased in the trophoblast population (1.05, 1.27 and a maximum of 1.52; p < 0.001) after incubation with the highest concentrations of the three hormones compared with untreated cells.

Effect of All Hormones in Combination on Radioiodide Uptake and Iodide Transporter Expression

As shown in figure 5, the greatest overall increase in both ^{125}I uptake and NIS expression occurred following incubation of cells with a combination of progesterone, 17β-estradiol, prolactin and oxytocin at the concentrations previously shown to produce maximum effects on ^{125}I uptake. This increase in uptake occurred in a dose-dependent manner with increases of up to 82% being observed at the highest concentrations of the three hormones. Maximum net iodide uptake (83%) with the highest concentrations of the four hormones was also greater than that achieved by any other hormone or hormone combination tested. This increase is highly significant (p < 0.001) and was again accompanied by corresponding increases in NIS expression (1.56 at the highest concentrations of the four hormones; p < 0.001) compared with untreated controls, but no changes in PDS expression levels were observed.

Discussion

The findings demonstrate that the pregnancy-related hormones hCG, prolactin and oxytocin have the ability to significantly increase iodide uptake in placental primary cultures prepared from tissues obtained at term. They also show that these increases in uptake can be attributed to increased NIS expression in the placental cultures upregulated in response to incubation with those hormones. The ability of pregnancy-related hormones to influence ^{125}I uptake and NIS expression is obviously dependent on the presence and abundance of individual hormone receptors in late pregnancy placentas [31–34].

The possible contribution of cell proliferation to increased NIS expression shown in other cell lines of thyroid and breast [35] has not been assessed. Whether this would be significant at the 6-hour incubation time used in this study is open to question. Any such effect might be counteracted by the higher hormone concentrations affecting cell viability.

A strength of this study is in the application of primary placental cultures rather than cell lines as a model for the study of placental iodide transport. However, it must be stressed that the placental tissue was obtained from full-term pregnancies and, therefore, findings may not necessarily reflect events in early pregnancy; as previously stated, NIS expression was found in early pregnancy and remained relatively constant throughout gestation [6–8]. In addition, NIS was shown by both immunofluorescence and real-time PCR to be highly expressed in both first-trimester placental tissue and primary cultures from first-trimester trophoblasts [7, 8].

Studies in placental tissue sections at 8–10 weeks of gestation and in primary cultures of first-trimester placental trophoblasts [7] showed both NIS and PDS expression being unaffected by propylthiouracil (PTU). This is in contrast to earlier reports [11, 17] demonstrating PTU-induced decreases in NIS protein in both FRTL-5 and BeWo cells.

In an animal model, a 30-fold decrease in NIS expression has been reported in placental cells sampled in the third trimester compared to the first [4], while Di Cosmo et al. [6] found that NIS immunoreactivity in trophoblastic cells in the first trimester remained at relatively constant levels throughout gestation and Li et al. [9] showed that NIS mRNA expression was low at 6 weeks and peaked at 12 weeks of gestation. The timing of placental sample collection (i.e. at delivery) may also explain the relatively small increase in NIS expression observed in placental primary cultures in this study compared to that found in cell lines [4, 9]. While some previous reports have used carcinoma-transformed cell lines [9, 16–17], our use of fresh tissue samples to produce cultures on which uptake and real-time PCR were performed is more likely to approximate conditions in vivo. These cultures were also derived from more than one placenta, thus eliminating the possibility of individual genetic factors affecting the outcomes. Whether this factor also explains the failure of hormonal preparations to induce PDS expression in placental primary cultures remains unanswered. Although the increases in iodide uptake are accompanied by elevated NIS expression, our results pose a number of unanswered questions. As the cells were not preloaded with iodide before incubation with hormones, non-specific anionic iodide uptake might have contributed to the observed increase in ^{125}I uptake. However, the absolute values for increased ^{125}I uptake and NIS expression both total (82% increase) and net (83% increase) as well as NIS ratio (1.52) were greatest when a combined hormone preparation was tested (as in fig. 5) supporting a significant role for NIS, as distinct from passive uptake. While prolactin and oxytocin do increase uptake and NIS expression individually, we cannot explain the amplified increases observed when these hormones are used in combination with the steroids 17β-estradiol and progesterone which themselves produce no significant effect on uptake or expression. A similar synergism was reported by Tazebay et al. [20] in studies on breast cancer cells. The increase in iodide uptake observed in our study is of course the sum of both uptake and efflux. Interestingly, support for the finding of estrogen and progesterone synergism with oxytocin and prolactin in promoting ^{125}I uptake and NIS expression in placental cells is supported by the suggestion that ^{125}I uptake and NIS expression in both rat lactating mammary glands and human breast tumors are potentiated by oxytocin and prolactin [18]. It appears that estrogens need to be above a certain threshold for oxytocin and prolactin to enhance mammary gland NIS [35]. While it is well established that in the thyroid NIS-mediated transport of iodide is driven by the electrochemical sodium gradient generated by the Na(+)/K(+)-ATPase [36], it remains unclear through which pathway 17β-estradiol may act to influence NIS expression [37]. It has been shown that in common with thyroid [38], enhancement of NIS expression and ^{125}I uptake by retinoids (RA) in lactating breast tissue can be diminished by 17β-estradiol treatment [39], which is in contrast to the positive findings demonstrated by Tazebay et al. [20] and in this study, albeit in different tissues. Therefore, it remains unclear through which pathway estrogens may act to influence NIS expression.

Although efflux of anionic ^{125}I was not studied in primary placental cell cultures, previous studies in whole placental tissue have shown that this may have been a contributory factor as placental efflux was midway between that observed in thyroid or non-thyroidal tissues [15].

These findings concur with previous work on the placenta identifying the NIS as the main transporter involved in uptake of iodide by the placenta [4–8, 19], while identifying a number of hormones as well as oxygen concentration [40] which affect both the expression levels and uptake by this transporter within the placenta. Blockade of iodide uptake by potassium perchlorate significantly decreased uptake by the trophoblast cells while not affecting NIS expression, demonstrating that NIS is mainly responsible for uptake of iodide to the placenta from the maternal circulation. This mechanism of uptake appears similar to that in the thyroid in which NIS function is competitively inhibited by perchlorate [35], rather than mediated at the DNA level.

The uptake of iodide by other tissues, including mouse and human mammary tissue and thyroid, can be influenced by the pregnancy-related hormones prolactin, 17β-estradiol and oxytocin [18–20]. Our studies of the effect of these hormones on placental tissue found that, individually, oxytocin ($p < 0.001$) and, to a lesser extent, prolactin ($p < 0.01$) have significant effects on iodide uptake as well as increased NIS expression. Neither 17β-estradiol nor progesterone had any significant effect on either uptake or NIS expression levels. hCG has been shown to effect iodide uptake in two placental choriocarcinoma lines [16, 17]. Our results support this finding, with hCG-treated trophoblasts exhibiting the greatest overall increase in iodide uptake of all individual hormones. Presumably, the effects of hCG would be even more significant in the first trimester of pregnancy in view of the peaks of its activity occurring at that time of gestation. Unfortunately, possible effects of 17β-estradiol or progesterone on hCG-stimulated ^{125}I uptake or NIS expression were not tested.

Findings in the present study highlight the similarities between placental iodide transport and NIS-mediated thyroidal iodide transport [30]. Coupled with other reports, which used placental cell lines or early invasive trophoblasts [7, 16, 17], our results support the hypothesis that NIS is primarily responsible for placental iodide uptake. Potassium perchlorate is a potent inhibitor of thyroidal iodide uptake [39] and we have shown it to similarly inhibit placental iodide uptake. While there is experimental evidence of low iodide intake resulting in increased NIS expression in an animal model [14], the authors are not aware of any published work implicating high iodide intake downregulating NIS as has been described in the thyroid [38]. Among the pregnancy-associated hormones studied, we have identified in particular hCG, oxytocin and prolactin as the most likely candidates in promoting uptake of iodide by the placenta. Although 17β-estradiol and progesterone do not themselves promote placental iodide uptake or NIS expression, they appear to exert a synergistic action with prolactin and oxytocin and may be a modulator of oxytocin and prolactin action in the placenta. Whether 17β-estradiol or progesterone is the primary effector remains to be elucidated.

The results suggest that transport of iodide arising from maternal dietary intake or perhaps intraplacental deiodination [13] is at least in part under the control of pregnancy hormones. Such transport may direct iodide to placental storage as we have previously shown [15]. However, the availability to the fetus of such anionic iodide remains to be determined. Thus, the peptide and steroidal endocrine environment has the potential to protect the fetus from iodine deficiency during the most vulnerable developmental periods such as early gestation where maximal hCG concentrations occur or at delivery when levels of prolactin and oxytocin peak.

Disclosure Statement

The authors have no conflicting interests.

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