The identification of irisin in human cerebrospinal fluid: influence of adiposity, metabolic markers, and gestational diabetes

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Submitted 7 June 2013; accepted in final form 5 January 2014

Piya MK, Harte AL, Sivakumar K, Tripathi G, Voyias PD, James S, Sabico S, Al-Daghi NM, Saravanan P, Barber TM, Kumar S, Vatish M, McTernan PG. The identification of irisin in human cerebrospinal fluid: influence of adiposity, metabolic markers, and gestational diabetes. Am J Physiol Endocrinol Metab 306: E512–E518, 2014. First published January 7, 2014; doi:10.1152/ajpendo.00308.2013.—Peripheral action of irisin improves glucose homeostasis and increases energy expenditure, with no data on a central role of irisin in metabolism. These studies sought to examine I) presence of irisin in human cerebrospinal fluid (CSF) and in maternal subjects across varying adiposities with or without gestational diabetes (GDM), and II) their respective neonate offspring. CSF, serum, and neonatal cord serum were collected from 91 pregnant women with and without GDM attending for an elective cesarean section [body mass index (BMI): 37.7 ± 7.6 kg/m2; age: 32 ± 8.3 yr]. Irisin was assessed by ELISA and correlated with biochemical and anthropometric data. Irisin expression was examined in human hypothalamus by immunohistochemical staining. Serum irisin in pregnant women was significantly lower in nonobese compared with obese and GDM subjects, after adjusting for BMI, lipids, and glucose. Irisin was present in neonatal cord serum (237 ± 8 ng/ml) and maternal CSF (32 ± 1.5 ng/ml). CSF irisin correlated positively with serum irisin levels from nonobese and obese pregnant women (P < 0.01), with CSF irisin significantly raised in GDM subjects (P < 0.05). Irisin was present in human hypothalamic sections in the paraventricular neurons, colocalized with neuropeptide Y. Irisin was detectable in CSF and in paraventricular neurons. Maternal serum irisin was lower in nonobese pregnant women after adjusting for BMI and a number of metabolic parameters. These studies indicate that irisin may have a central role in metabolism in addition to the known peripheral role. Further studies investigating the central action of irisin in human metabolic disease are required.

EMERGING DATA SUGGEST THAT a newly discovered polypeptide hormone, irisin, a cleaved secreted form of fibronectin type III domain containing 5 (FNDC5), has the potential to increase energy expenditure and improve glucose homeostasis in humans (4, 16, 31, 34). This is particularly significant, since irisin can induce the transformation of white adipocytes into “beige” or “brite” adipocytes, which can ultimately lead to increased mitochondrial respiration (4, 34), with implications for weight loss. Therefore, such studies suggest the potential therapeutic applications of irisin not only in use for weight loss but also to improve glucose metabolism (4). Subsequent research has also revealed that the function of irisin appears to fall beyond its original role noted in muscle (4, 9, 13, 21, 23), and the administration of exogenous irisin could theoretically increase energy expenditure during or after weight loss. Recent studies have shown that irisin may also act as an adipokine (21, 25) as well as a potential “neurokine” (9, 12). Although the role of irisin in the brain is unclear, analysis has revealed that FNDC5 knockdown in murine embryonic stem cells reduces neurogenesis (11), whereas pharmacological doses of irisin increase proliferation of mouse hippocampal neuronal cells (20). Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC1α) regulates FNDC5 expression, and recent studies have shown an increase in FNDC5 expression in mouse hippocampus neuronal cells in response to endurance exercise that is reduced in PGC1α knockdown mice (33). Given that exercise is known to improve neurogenesis and slow the progression of neurodegenerative diseases (29), irisin may have both central and peripheral functions that could be used for therapeutic use in combination with exercise.

To determine the therapeutic potential of irisin, studies have subsequently focused on the peripheral changes in irisin in different clinical metabolic states. These studies have highlighted conflicting reports on changes in circulating irisin levels in patients with insulin resistance states such as obesity, type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM) (3, 5, 12, 17, 21, 22, 24, 28, 30). Specifically, some reports have noted an increase in circulating irisin, observing a negative correlation with hemoglobin A1c, body mass index (BMI), lipids, and irisin or no change in irisin with insulin sensitivity (12, 24, 28, 30). Serum irisin in children, especially girls, has been shown to have a significant negative correlation with fasting blood glucose, suggesting a possible link of irisin to glucose homeostasis from an early age (1).

We examined cerebrospinal fluid (CSF), serum, and cord blood levels of irisin in obese patients with and without GDM undergoing cesarean section under spinal anesthesia to test the
hypothesis that irisin has both a peripheral and central role in metabolic regulation of energy homeostasis and, moreover, that metabolic disease status may affect the central and peripheral action of irisin. Hence, the aim of this study was to firmly establish the presence of irisin in human CSF as well as banked human hypothalamic sections and subsequently to establish the relationship between CSF and serum irisin and the influences of adiposity, insulin resistance status, leptin, and lipid profile. These studies also examined the changes in serum irisin between matched maternal serum and neonate cord blood, and the concordance with biochemical and anthropometric factors.

**MATERIALS AND METHODS**

Individuals undergoing elective cesarean section, under local spinal anesthesia, were recruited and consented with approval of the Coventry and Warwickshire Research Ethics Committee (ref. 10/H1211/4). Exclusion criteria included malignancy, acute or chronic renal or liver disease, neurological disorders, the use of immunosuppressants, or current or recent use of systemic high-dose corticosteroids, antibiotics, or weight-modifying medication. Patients with a C-reactive protein level above 10 mg/dl were also excluded. BMI was calculated for pregnant women at 12 wk gestation. *P* < 0.05, **P* < 0.01, and ***P* < 0.001 compared with GDM. ###P* < 0.001 compared with pregnant obese. In the nonpregnant cohort, $P$ < 0.05, $SP$ < 0.01, and $SSSP$ < 0.001 compared with nonpregnant lean.

**Table 1. Baseline clinical and metabolic data of pregnant and nonpregnant women**

<table>
<thead>
<tr>
<th></th>
<th>Nonobese</th>
<th>Obese</th>
<th>GDM</th>
<th>Lean</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>n</em></td>
<td>34</td>
<td>39</td>
<td>18</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Age, yr (means±SD)</td>
<td>32.0 ± 6.0</td>
<td>32.5 ± 5.6</td>
<td>34.4 ± 6.7</td>
<td>42.1 ± 6.1</td>
<td>46.8 ± 7.7</td>
</tr>
<tr>
<td>BMI* kg/m² (means±SD)</td>
<td>23.4 ± 2.0***</td>
<td>33.7 ± 4.4*</td>
<td>31.2 ± 6.1</td>
<td>22.6 ± 1.7</td>
<td>34.3 ± 3.9***</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>4.3 ± 0.6</td>
<td>4.3 ± 0.1*</td>
<td>4.8 ± 0.3</td>
<td>4.6 ± 0.1</td>
<td>5.4 ± 0.2***</td>
</tr>
<tr>
<td>Insulin, pmol/l</td>
<td>11.9 ± 0.3</td>
<td>17.8 ± 1.8</td>
<td>16.4 ± 3.4</td>
<td>66.9 ± 13.4****</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.33 ± 0.04</td>
<td>0.52 ± 0.05</td>
<td>0.48 ± 0.1</td>
<td>0.48 ± 0.1</td>
<td>2.4 ± 0.4***</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>6.9 ± 1.0</td>
<td>6.5 ± 0.2</td>
<td>6.1 ± 0.3</td>
<td>4.7 ± 0.2</td>
<td>5.4 ± 0.2***</td>
</tr>
<tr>
<td>TG, mmol/l</td>
<td>2.6 ± 0.1*</td>
<td>2.7 ± 0.2*</td>
<td>3.5 ± 0.3</td>
<td>0.8 ± 0.1</td>
<td>1.4 ± 0.3**</td>
</tr>
<tr>
<td>HDL, mmol/l</td>
<td>1.7 ± 0.1**</td>
<td>1.7 ± 0.1**</td>
<td>1.3 ± 0.1</td>
<td>1.8 ± 0.1</td>
<td>1.4 ± 0.1*</td>
</tr>
<tr>
<td>LDL, mmol/l</td>
<td>4.0 ± 0.2*</td>
<td>3.6 ± 0.2</td>
<td>3.1 ± 0.3</td>
<td>2.5 ± 0.2</td>
<td>2.9 ± 0.2</td>
</tr>
<tr>
<td>Leptin, ng/ml</td>
<td>24.5 ± 2.9**</td>
<td>41.8 ± 3.3</td>
<td>38.3 ± 2.6</td>
<td>25.1 ± 4.3</td>
<td>46.8 ± 4.6***</td>
</tr>
<tr>
<td>Irisin, ng/ml</td>
<td>805 ± 53</td>
<td>791 ± 52</td>
<td>802 ± 88</td>
<td>781 ± 49</td>
<td>795 ± 83</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE except for age and body mass index (BMI), which are expressed as means ± SD; *n*, no. of subjects. GDM, gestational diabetes mellitus; HOMA-IR, homeostasis assessment model insulin resistance; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein.

**Table 2. Baseline comparison of neonate cord blood parameters across groups of pregnant women**

<table>
<thead>
<tr>
<th></th>
<th>Nonobese</th>
<th>Obese</th>
<th>GDM</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>n</em></td>
<td>34</td>
<td>39</td>
<td>18</td>
</tr>
<tr>
<td>Birth wt, kg</td>
<td>3.6 ± 0.05</td>
<td>3.6 ± 0.08*</td>
<td>3.4 ± 0.17</td>
</tr>
<tr>
<td>Cord glucose, mmol/l</td>
<td>3.7 ± 0.07**</td>
<td>3.9 ± 0.07*</td>
<td>4.5 ± 0.36</td>
</tr>
<tr>
<td>Cord insulin, pmol/l</td>
<td>9.0 ± 0.8</td>
<td>11.4 ± 2.1</td>
<td>12.8 ± 2.3</td>
</tr>
<tr>
<td>Cord cholesterol</td>
<td>16.0 ± 0.07</td>
<td>17.7 ± 0.06</td>
<td>17.7 ± 0.13</td>
</tr>
<tr>
<td>Cord TG</td>
<td>0.21 ± 0.02</td>
<td>0.22 ± 0.01</td>
<td>0.25 ± 0.02</td>
</tr>
<tr>
<td>Cord HDL</td>
<td>0.81 ± 0.04</td>
<td>0.71 ± 0.03</td>
<td>0.69 ± 0.06</td>
</tr>
<tr>
<td>Cord LDL</td>
<td>0.74 ± 0.03*</td>
<td>0.87 ± 0.04</td>
<td>0.93 ± 0.07</td>
</tr>
<tr>
<td>Cord leptin, ng/ml</td>
<td>3.5 ± 0.4</td>
<td>5.9 ± 0.8</td>
<td>4.1 ± 0.3</td>
</tr>
<tr>
<td>Cord irisin, ng/ml</td>
<td>225 ± 11</td>
<td>235 ± 16</td>
<td>263 ± 15</td>
</tr>
</tbody>
</table>

Values expressed as means ± SE; *n*, no. of subjects. *P* < 0.05 and **P* < 0.01 compared with GDM.
subjects, as described in Table 1. Serum leptin levels positively correlated with BMI \( (r = 0.53, P < 0.001) \), insulin levels \( (r = 0.51, P < 0.001) \), and HOMA-IR \( (r = 0.5, P < 0.001) \) across the cohort of pregnant women. Subsequent analysis, controlling for BMI, indicated serum leptin remained correlated with both insulin \( (r = 0.35; P = 0.002) \) and HOMA-IR \( (r = 0.37, P = 0.006) \) in the pregnant women.

Irisin serum levels in women. Serum irisin levels were similar in pregnant women from the nonobese \((805 \pm 53 \text{ ng/ml})\), obese \((791 \pm 52 \text{ ng/ml})\), and GDM \((802 \pm 88 \text{ ng/ml})\); Table 1) groups. Serum irisin levels were similar in a separate cohort of nonpregnant lean \((781 \pm 49 \text{ ng/ml})\) and obese \((795 \pm 83 \text{ ng/ml})\) women. Analysis of the pregnant subjects revealed that there was a significant inverse correlation of BMI with serum irisin \( (r = -0.25, P = 0.026) \) (Fig. 1A). In the pregnant cohort, serum irisin levels were also positively correlated with glucose \( (r = 0.40, P < 0.001) \), insulin \( (r = 0.26, P = 0.048) \), HOMA-IR \( (r = 0.32, P = 0.013) \), total cholesterol \( (r = 0.35, P = 0.002) \), TG \( (r = 0.33, P = 0.003) \), LDL \( (r = 0.24, P = 0.036) \), and HDL \( (r = 0.27, P = 0.017) \). Analysis using ANCOVA revealed that serum irisin was significantly lower in nonobese pregnant women compared with the obese pregnant and GDM women after adjusting for BMI, serum lipids, and glucose \( (P < 0.01) \), whereas there was no significant difference between serum irisin levels across groups when only adjusting for serum lipids or glucose.

Irisin cord serum levels in neonates. Baseline biochemical data were collated as described in Table 2. Irisin levels were significantly lower in cord serum samples compared with adult irisin levels \((
\text {neonate irisin: } 237 \pm 8 \text{ ng/ml}; \text{maternal irisin: } 799 \pm 35 \text{ ng/ml}; P < 0.001; \text{Tables 1 and 2})\). Maternal serum irisin levels appeared to correlate with cord serum irisin levels \( (r = 0.28, P = 0.015) \) (Fig. 2A). No further correlations were noted between neonatal serum irisin, taking into account neonatal biochemical data as well as birth weight or maternal BMI. Cord serum irisin levels were also noted to have a positive correlation with cord serum irisin levels \( (r = 0.24, P = 0.035) \); Fig. 2B).

Irisin CSF levels in women. Cerebrospinal irisin levels were \(32 \pm 1.5 \text{ ng/ml}\). The levels in the CSF were therefore \(20-25\)-fold lower than the maternal serum. CSF irisin did not correlate with BMI, lipids, or HOMA-IR. GDM status significantly increased CSF irisin levels compared with nonobese women \((39 \pm 2.8 \text{ ng/ml})\) \( (P < 0.05) \).
From the entire cohort, CSF irisin levels positively correlated with serum irisin levels \((r = 0.32, P = 0.006)\) (Fig. 3A). This positive correlation was significant in the nonobese and obese groups (Fig. 3, B and C), but the correlation was lost with GDM status (Fig. 3D). In contrast to irisin serum data, there was no correlation between CSF irisin levels and BMI \((r = 0.06, \text{not significant})\) (Fig. 1B).

**Expression of irisin in the human hypothalamus.** Immunohistochemistry showed the presence of irisin in the neuronal cells in the human hypothalamus from donated samples obtained from a human tissue bank (Fig. 4A). Irisin was observed to be concentrated in the paraventricular nucleus (PVN) within the neurons, which were dual stained with NPY (Fig. 4D). Skeletal muscle was used as a positive control for irisin expression (Fig. 4E).

**DISCUSSION**

From this study, we have identified that irisin is detectable in CSF, and CSF levels are higher in GDM mothers compared with nonobese and obese pregnant mothers. We have also identified that irisin was detectable in human hypothalamic sections, concentrated around the PVN region. Serum irisin in the pregnant women was positively correlated with glucose, insulin, HOMA-IR, total cholesterol, TG, LDL, and HDL, and the serum irisin levels in the nonobese women were significantly lower than the obese and GDM women after correction for BMI, serum lipids, and glucose. Irisin was also detectable in neonatal cord serum, with no differences in levels between groups.

![Fig. 2. Correlations of neonatal cord irisin with maternal serum irisin and cord leptin.](image)

A shows a significant positive correlation between neonatal cord irisin and maternal serum irisin. B shows a significant positive correlation between neonatal cord irisin and cord leptin \((r \) represents the correlation coefficient for the linear curve with significant \( P \) values as shown).
On the basis of this study, CSF irisin appears 20- to 25-fold lower than circulating serum levels. This still remains relatively high, particularly since previous CSF-to-serum ratios for human adipokines have shown a 1:100-fold ratio for leptin, 1:1,000-fold ratio for adiponectin, and 1:100-fold ratio for resistin (14, 15). The irisin CSF levels, although much lower than concentrations in the periphery, are sufficient for activation of neural pathways and signaling in the hypothalamic nuclei for proteins like leptin (7, 35).

To address whether irisin may influence energy expenditure, immunohistochemical analysis was undertaken to detect the presence of irisin in banked human brain tissue. From the immunohistochemistry, irisin was observed to be present in the human hypothalamus, with concentrated expression of irisin in neuronal cells of the PVN, which also express NPY. There may be a cross-reactivity between irisin and FNDC5, but the presence in these neurons is particularly relevant, since the PVN receives input from the arcuate nucleus, a region of the brain containing key appetite-regulating pathways via NPY neurons (8).

Analysis of irisin levels also observed a positive linear correlation between serum and CSF irisin, with this correlation being lost in the GDM group. However, in the GDM group, CSF irisin levels were significantly higher when compared with the nonobese group. This increase in irisin CSF could suggest a compensatory mechanism, in GDM subjects, with a metabolically compromised state, as suggested previously for serum irisin (12). Furthermore, the positive linear correlation between serum and CSF irisin suggests that the detected CSF irisin may be derived from the periphery and that the blood-brain barrier (BBB) limits access of irisin in the lean and obese states.

Taken together, the current serum/CSF data would suggest a transport mechanism for irisin crossing the BBB, rather than simple osmosis, but it is unknown what may mediate this mechanism. Ideally, for an active transport mechanism, it would be important to establish irisin receptor presence on human endothelial cells of the choroid plexus. This region controls entry of proteins through the BBB and is where prior studies have identified functional leptin receptors (19). If irisin could be transported from blood to CSF by receptor-mediated transcytosis, similar to a mechanism proposed for leptin, this would support the concept that CSF entry may be facilitated at lower irisin levels in nonobese subjects, which may support body energy homeostasis and enhance thermogenesis, again, in

Fig. 4. Immunohistological staining of human hypothalamus. A: immunohistological staining of human hypothalamus with positive staining for irisin (1:200 dilution) (brown; ×400 magnification). B: negative staining for human hypothalamus with irisin [1:200 irisin with 1:50 recombinant human (rh) irisin; ×400 magnification]. C: human hypothalamus with positive staining for neuropeptide Y (NPY) (1:500 dilution) (purple; ×400 magnification), which highlights the area of the paraventricular nucleus. D: dual staining of irisin (purple) and NPY (brown) (×400 magnifications); note the darker dual-stained areas (red arrow) and dendritic projections of the neural cells and cytoplasmic expression of irisin. E: human skeletal muscle with positive staining for irisin (1:200 dilution) (brown; ×400 magnification). F: negative staining for human skeletal muscle with irisin (1:200 irisin with 1:50 rh irisin; ×400 magnification).
that irisin has both peripheral and central functions. Further
GDM status. As such, these findings strengthen the concept
in the hypothalamus. Irisin CSF levels appeared correlated
appears colocalized with NPY in the neuronal cells of the PVN
populations. In summary, irisin is present in human CSF and
we believe that these data may be extrapolated to different
found to be similar to the levels in pregnant women, and serum
obtained from a cohort of pregnant women, which may not be
weakness of this study is that the serum and CSF samples were
also noted for leptin, although at significantly lower levels, and cord
irisin levels positively correlated with cord leptin. Such an
association suggests the possibility that irisin levels could be
predetermined in utero by maternal influences, as previously
noted for leptin and adiponectin (10, 26). Our data also high-
lighted that the level of serum irisin in pregnancy was not
solely related to this state, since findings were comparable in
the nonpregnant state, affirming previous findings using the
same irisin ELISA kit from Phoenix Europe (1, 30).
Assessment of serum irisin levels highlighted that there was
no significant difference between nonobese, obese, and GDM
groups, although a negative correlation between BMI and
and serum irisin was noted. Further analysis using ANCOVA was
undertaken and demonstrated that the serum irisin levels were
significantly lower in the nonobese pregnant group compared
with the obese pregnant and GDM groups, after adjusting for a
combination of BMI, serum lipids, and serum glucose. Fur-
thermore, in addition to supporting the emerging concept of
irisin resistance in metabolic disease, this may partly explain
the conflicting reports on the serum levels of irisin in different
metabolic disease states (3, 5, 12, 17, 21, 24, 28, 30).
This is the first study to show presence of irisin in human
CSF as well as in the human hypothalamus. Serum samples
have been collected from three different groups of pregnant
women: GDM, obese, and nonobese groups. The strength of
this study is that CSF samples and neonatal cord serum have
also been collected from the corresponding mothers, allowing
for a detailed study of the possible role of irisin in humans as
well as the possible influences of metabolic state. The main
weakness of this study is that the serum and CSF samples were
obtained from a cohort of pregnant women, which may not be
representative of a nonpregnant population. The BMI of the
women was calculated at 12 wk gestation to avoid the effect of
weight gain in pregnancy on the BMI, whereas the serum and
CSF samples were collected at the time of delivery. However,
given that serum irisin levels from nonpregnant women were
found to be similar to the levels in pregnant women, and serum
leptin levels were positively correlated to the calculated BMI,
we believe that these data may be extrapolated to different
populations. In summary, irisin is present in human CSF and
appears colocalized with NPY in the neuronal cells of the PVN
in the hypothalamus. Irisin CSF levels appeared correlated
with serum levels and influenced by metabolic markers and
GDM status. As such, these findings strengthen the concept
that irisin has both peripheral and central functions. Further
studies are required in nonpregnant populations, as well as to
examine the direct influence of irisin on central metabolism.
and whether obesity-coupled T2DM status leads to irisin resistance
in a similar fashion noted for leptin.

ACKNOWLEDGMENTS
We thank the operative Obstetric theater staff and anesthesia
teachers at University Hospitals Coventry and Warwickshire (UHCW) NHS Trust for the
provision of consented samples. We also thank Birmingham Science City. We also acknowledge UHCW NHS Trust, the Rowlands Trust, Coventry District
Charitable Trust, and the British Heart Foundation for support.

DISCLOSURES
M. Vatish and P. G. McTernan are the guarantors of this work, had full
access to all the data, and take full responsibility for the integrity of data and
the accuracy of data analysis.

AUTHOR CONTRIBUTIONS
Author contributions: M.K.P., M.V., and P.G.M. conception and design of
research; M.K.P., A.L.H., K.S., P.D.V., S.J., and P.G.M. performed experi-
ments; M.K.P., S.S., N.M.A.-D., M.V., and P.G.M. analyzed data; M.K.P.,
M.V., and P.G.M. interpreted results of experiments; M.K.P. prepared figures;
M.K.P., A.L.H., and P.G.M. drafted manuscript; A.L.H., G.T., N.M.A.-D.,
P.S., T.M.B., S.K., M.V., and P.G.M. edited and revised manuscript; M.V. and
P.G.M. approved final version of manuscript.

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