PLACENTAL IGF1R-PI3K/AKT PATHWAY AND ITS RELATIONSHIP TO IDIOPATHIC BIRTH WEIGHT ALTERATIONS

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INTRODUCTION

Alterations in fetal growth lead to neonatal health risks and favor metabolic diseases during adult life (1). Therefore, the study of birth weight determination and its modifications is crucial for metabolic diseases prevention. Placental growth is a key factor in fetal growth (2). It has been suggested that insulin and the IGF (Insulin-like growth factor) system play an important role in fetal growth and placental development and function (3). Although insulin and IGFs in the umbilical cord blood have been associated to birth weight (4), the roles of placental IGF1 and Insulin receptors (IGF1R and IR), and the PI3K/Akt signaling pathway, shared by both receptors, are not fully elucidated.

OBJECTIVE

We aimed to analyze protein expression of insulin/IGF receptors and activation of the PI3K/Akt pathway in relation to placental weight and birth weight.

METHODS

Transversal comparative study in placentas from healthy mothers of term newborns SGA, AGA and LGA (small, adequate and large for gestational age) (n=20 per group). Protein expression of IR, IGF1R and phosphorylation of signaling molecules were analyzed by Western Blot.

RESULTS

IGF1R expression decreased 20% significantly in SGA compared to control AGA, and positively correlated with placental weight (r=0.34, p=0.007) and birth weight (r=0.285, p=0.027). IR protein expression was not modified between groups. Phosphorylation of PDK1, main kinase for Akt activation, decreased 40% in both SGA and LGA compared to control. In line with this, we observed a nearly 30% decrease in total Akt in SGA and LGA compared to AGA. PDK1-dependent phosphorylation pAkt-Thr308 showed a tendency, albeit not significant, to decrease in SGA and LGA, while pAkt-Ser273 did not differ between groups.

Table 1. Clinical and anthropometric characteristics of mothers of SGA, AGA and LGA newborns.

	SGA mothers (n =20)	AGA mothers (n = 20)	LGA mothers (n = 20)	F/H#	p
Age (years)	24.5 ±4.7	24.5 ± 5.6	26.9 ±4.7	1.5	0.2322
Pregestational Weight (Kg)	54.9 ± 10.6 ¤	57.1 ± 9.3 ¥	75.9 ±20.8 *+	11.7	**<0.0001**
Height (m)	1.5 ± 0.07	1.5 ± 0.04	1.6 ± 0.06¤ *+	2.9	0.0612
Pregestational BMI (Kg/m^2)	23.4 ± 5.3 ¥	23.9 ± 3.9 ¤	30.0 ± 9.0 ¢ *+	5.9	**0.0051**
Gestational weight gain (kg)	12 (10 - 13)	12 (10 - 18)	12 (10 - 15)	2.1#	0.3495

Mean ± SD; median (quartile range); F, F value for ANOVA; H, H value of Chi-squared for Kruskal-Wallis. ¤, n=19; ¥, n=18; §, n=16; ¢, n=17. *p<0.05 compared to control AGA. +p<0.05 compared to SGA.

Table 2. Clinical and anthropometric characteristics of SGA, AGA and LGA newborns.

	SGA (n = 20)	AGA (n = 20)	LGA (n = 20)	F/H#	*p*-value
Baby's gender (Male/Female)	9 /11	12/8	12 /8	ND	ND
Delivery method (Vaginal/C-section)	9 /11	13 /7	8 /12	ND	ND
Gestacional age (wk)	38.2 ± 1.1	38.7 ± 1.1	39.4 ± 0.9+	6.1	**0.0065**
Placental weight (g)	400.4 ± 64.3 ¤*	610.4 ± 23.8	750.6 ±118.7*+	60.6	**<0.0001**
Birthweight (g)	2297 (2089-2403)*	3273 (2915-3358)	3915 (3815-4167) *+	52.5#	**<0.0001**
Birth lenght (cm)	45.7 ± 2.5*	50.9 ±2.0	52.7 ± 2.1*+	53.6	**<0.0001**
Cephalic perimeter (cm)	32.225 ± 1.6*	34.7 ± 1.6	36.5 ± 1.3*+	39.6	**<0.0001**
Thoracic perimeter (cm)	29.5 (28-31) *	34 (32-34)	35 (35 - 37) *+	45.4#	**<0.0001**
Abdominal perimeter (cm)	27.3 ± 2.0*	30.8 ±1.6	34.1 ± 2.2*	60.2	**<0.0001**

Mean ± SD; median (quartile range); F, F value for ANOVA; H, H value of Chi-squared for Kruskal-Wallis. N.D., not determined. ¤ n=19. *p<0.05 compared to control AGA. Mean ± SD; median (quartile range); F, F value for ANOVA; H, ¤ n=19. *p<0.05 compared to control AGA. +p<0.05 compared to SGA.

Sources of Research Support: University of Guanajuato (0095/13), FOMIX CONACYT- Guanajuato State Government (GTO-2012-C03-195238). MLLVM was recipient of a postdoctoral CONACYT Fellowship Scholarship (CVU: 217876).

Figure 1. IGF1R protein expression (A, B) and its correlation with placental (C) and birth weight (D).

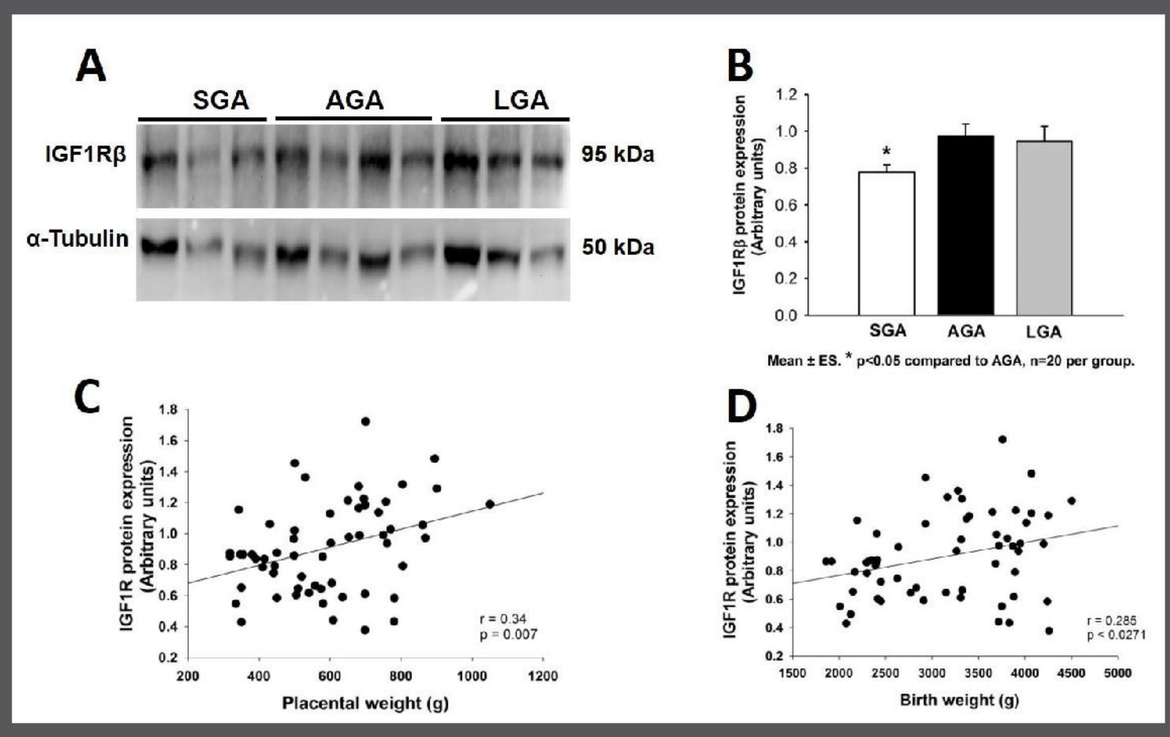


Figure 2. Protein expression and activation of the PI3K/Akt pathway. PDK1 phosphorilation (A), total Akt (B) Akt-Thr308 phosphorylation (C) and Akt-Ser473 phosphorylation (D). Mean ± ES. * p<0.05 compared to AGA, n=20 per group.

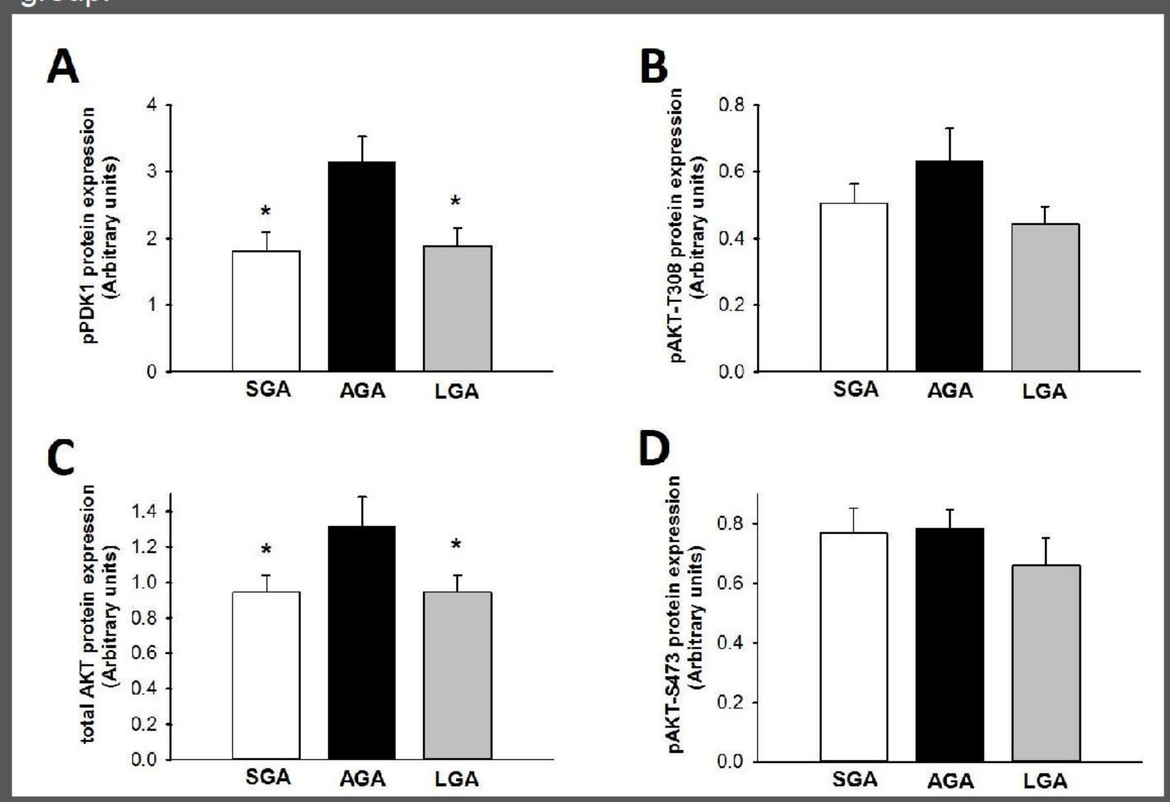
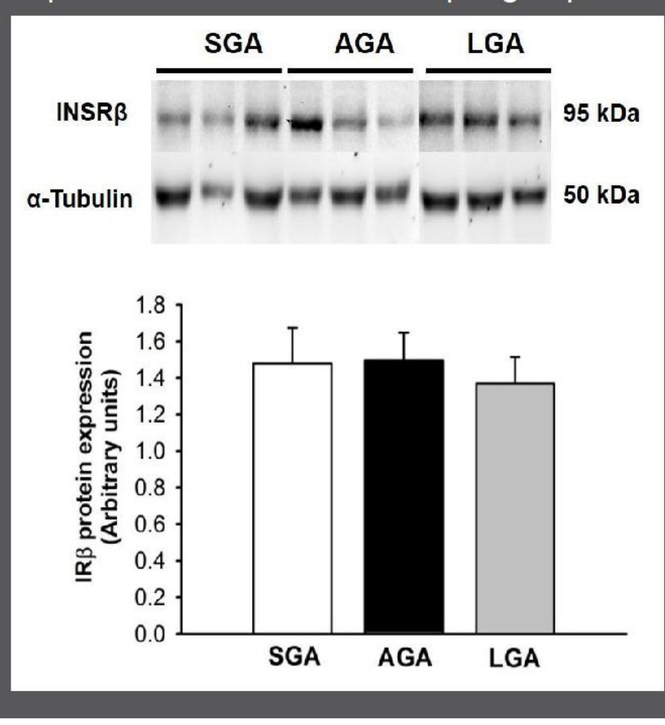


Figure 3. Insulin receptor (INSR) protein expression. Mean ± ES. n=20 per group.



CONCLUSIONS

These results suggest PI3K/Akt pathway may be differentially regulated in SGA and LGA placentas, possibly related to decreased IGF1R expression in SGA, and perhaps other signaling pathways in LGA, consequently leading to alterations in birth weight.

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17 ECE 676--EP

Pituitary basic and neuroendocrinology

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DOI: 10.3252/pso.eu.17ece.2015

Poster presented at: ECE2015 16-20 May 2015 DUBLIN, IRELAND 17th EUROPEAN CONGRESS OF ENDOCRINOLOGY

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