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Research Article

The Modulating Action of ACP_1 Genetic Polymorphism on the Effect of Smoking upon Birth Weight

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Abstract:

Objectives: In a previous paper we have reported that the negative effect of smoking on birth weight is modulated by the activity of maternal cytosolic Low Molecular Weight Protein Tyrosine Phospatase (cLMWPTP), an enzyme encoded by Acid Phosphatase locus 1 (ACP_1). We have now examined (i) the effect of newborn cLMWPTP and (ii) and the effect of maternal age on the action of maternal cLMWPTP

Material and Methods: The data on 341 healthy puerperae and their newborn babies from the population of Penne have been re-examined.

Results: In smoking mothers, newborn babies with Low cLMWPTP enzymatic activity have a high risk of low birth weight. There is a significant correlation of birth weight with total neonatal cLMWPTP activity and with F isoform concentration but not with S isoform concentration

This effect is similar to that observed for maternal cLMWPTP activity. In smoking mothers, the action of maternal cLMWPTP on the relationship between smoking and birth weight is present in mothers aging more than 28 years only and it is lacking in smoking mothers aging 28 years or less.

Discussion: The effects observed could be related to interactions between toxic substances of cigarette smoking and cLMWPTP: low enzymatic activity could be less efficient in the detoxification of damaging substances from cigarette smoking. On the other hand, these substances could contribute to inactivate cLMWPTP resulting in negative metabolic and immunological effects depending on ACP1 genotype. Olders Smoking women could experience a cumulative effect of toxic substances from cigarette smoking that aggravate the damage of smoking on intrauterine growth. This could result in a more evident effect of cLMWPTP upon clinical manifestation in these women.

Conclusions: We suggest that also the action of other toxic environmental substances could be modulated by the activity of cLMWPTP with important effects on the risk of overt clinical manifestations.

Introduction: The negative effect of smoking on birth weight (BW) is well known. We have previously reported that this effect is modulated by the activity of maternal cytosolic Low Molecular Weight Protein Tyrosine Phospatase (cLMWPTP) an enzyme encoded by Acid Phosphatase locus 1 (ACP_1) [1]. In smoking mothers we reported a BW of 3070 gr in low cLMWPTP activity vs 3459 gr in medium-high activity; in non-smoking mothers BW was 3390 gr in low cLMWPTP activity mothers vs 3349 gr in medium-high cLMWPTP activity mothers.

In present note we report further data showing a similar effect of newborn cLMWPTP on the action of smoke upon BW. Moreover, we have examined the role of maternal age on the effect of maternal cLMWPTP upon BW.

ACP_1 genetic polymorphism: Cytosolic Low Molecular Weight Protein Tyrosine Phosphatase (cLMWPTP) is an enzyme controlled by the autosomal ACP_1 locus (ACP_1= Acid Phosphatase locus 1) with three common alleles: ACP_1*A, ACP_1*B, ACP_1*C. Correspondingly there are six genotypes showing the activities increasing in the order:
*A/*A<*A/*B<(*B/*B≤*A/*C)<*B/*C<*C/*C.The ACP_1*C/*C is very rare [2]. cLMWPTP may act as flavin-mono-nucleotide phosphatase and as tyrosine phosphatise. Catalysing the conversion of flavin-mononucleotide (FMN) to riboflavin, the enzyme may regulate the cellular concentration of flavin-adenine-dinucleotide (FAD), flavo-enzyme activity and energy metabolism. As phosphotyrosine phosphatase, the enzyme may regulate cellular growth and may modulatethe glycolytic rate through the control of insulin receptor activity and of band 3 protein phosphorylation status [3,4].

Enzymatic activity shows strong differences among genotypes suggesting that cLMWPTP may have an important role in the physiological variability of a large spectrum of cellular functions. The low activity *A/*A and *A/*B genotypes may favor glucose metabolism both through an enhancement of insulin action and through an increased phosphorylation of B3P that in turn activates aldolase, phosphofructokinase and glyceraldeide-3-phosphate dehydrogenase. Recently it has been shown that cLMWPTP specifically dephosphorylates the negative regulatory Tyr-292 of ZAP-70, counteracting the inactivation of ZAP-70 [5]. The ZAP-70 protein-tyrosine kinase plays a central role in signalling from the T cell antigen receptor suggesting that cLMWPTP strengthens T cell receptor signalling.

cLMWPTP protein is composed by two isoforms F and S that have different concentrations among ACP_1 genotypes [Table 1] and different biochemical properties suggesting different functions in vivo. The two isoforms have also a diverse localization in the cell [6]. Under the action of oxidative substances, the stability of F isoform is much lower as compared to that of S isoform [7,8].

F isoform		S isoform	
Genotypes	Total quantity (µg/mlRBC)	Genotypes	Total quantity (µg/mlRBC)
*B/*B	16.4	*C/*C	20.6
*A/*B	12.0	*A/*C	12.7
*B/*C	11.3	*B/*C	12.1
*A/*A	7.9	*B/*B	3.9
*A/*C	7.5	*A/*B	3.4
*C/*C	5.7	*A/*A	3.3

Table 1: F and S isoform concentrations in relation to ACP1 genotypes

Several studies have shown that redox status plays an important role in signal transduction involving protein-tyrosine phosphorylation. Reactive oxygen species have been identified as mediators of pathological manifestations after exposure to cigarette smoking [9]. Oxidative stress may alter the course of cellular response through modification of signal cascade. On the other hand cLMWPTP stability and activity are strongly influenced by oxidative substances [7,8] with important consequences at metabolic and immunological levels.

Material and Methods: We have reexamined the data of 341 health puerperae and of their newborn babies from the population of Penne considered in a previous study [1].

ACP_1 phenotype was determined analyzing RBC hemolysates by starch gel electrophoresis according to Spencer et al. [2]. By this method six phenotypes are detected with enzymatic activity increasing in the order: A<BA<B≤CA<CB<C. The polymorphism is determined by the presence of three codominant alleles *A,*B and *C at an autosomal locus.

T-test, variance analysis and correlation analysis were carried out by commercial software (SPSS).

Results:

We have previously shown that In smoking mothers BW shows the highest value in the presence of medium-high cLMWPTP activity (B,CA,CB and C phenotypes) and the lowest value in the presence of low cLMWPTP activity (A and BA phenotypes) suggesting that the offspring of these women have a high risk of low BW.

Figure 1 shows the relationship of BW with foetal cLMWPTP activity and maternal smoking. The pattern is similar to that observed with maternal ACP_1 [1]. In smoking mothers newborns carrying ACP_1 genotypes with low enzymatic activity have a high risk of low BW.

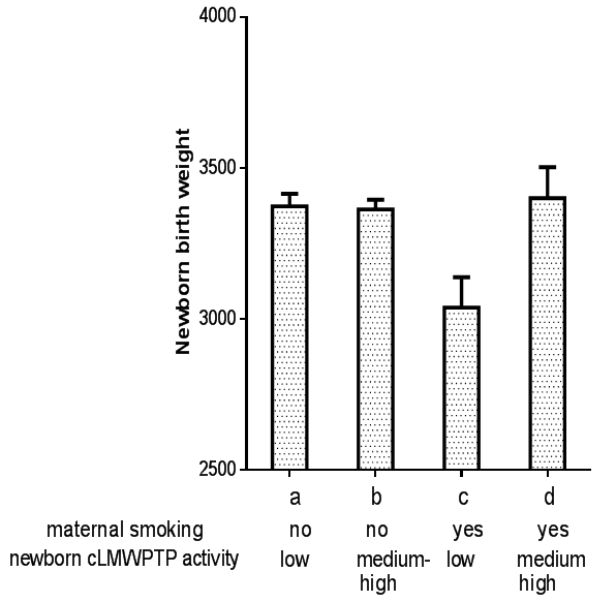


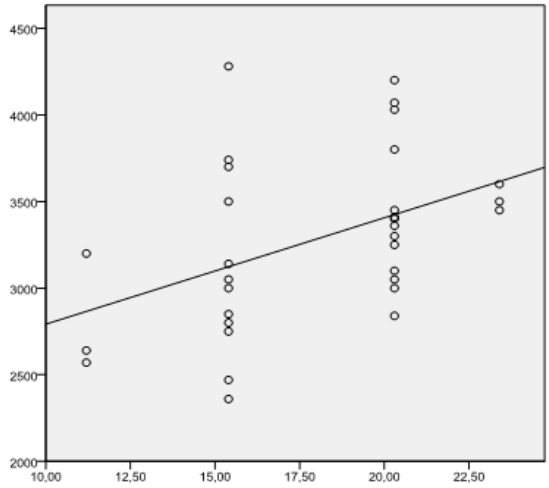
Figure 1: Birth weight (grams) of newborns from healthy puerperae in relation to newborn cLMWPTP activity and maternal smoking. Comparisions (t-test): a VS b p=N.S.; c VS d p<0.04

Table 2 shows the correlations between BW and newborn cLMWPTP activity parameters in smoking and in non-smoking mothers. In smoking mothers there is a statistically significant correlation of BW with total cLMWPTP activity and with F isoform concentration but not with S isoform concentration. Figure 2 depicts the pattern of correlation between BW and total newborn ACP_1 activity.

Smoking Mothers	
BW-total vs cLMWPTP activity	R=0.434 P=0.013
BW vs F isoform	R=0.360 P=0.043
BW vs S isoform	R=0.196 P=0.282
Non-smoking Mothers	
BW vs total cLMWPTP activity	R=-0.005 P=0.927
BW vs F isoform	R=0.005 P=0.923
BW vs S isoform	R=-0.012 P=0.832

Table 2: Correlation between BW and neonatal cLMWPTP parameters in smoking and non-smoking mothers

Maternal smoking yes:



Maternal smoking no:

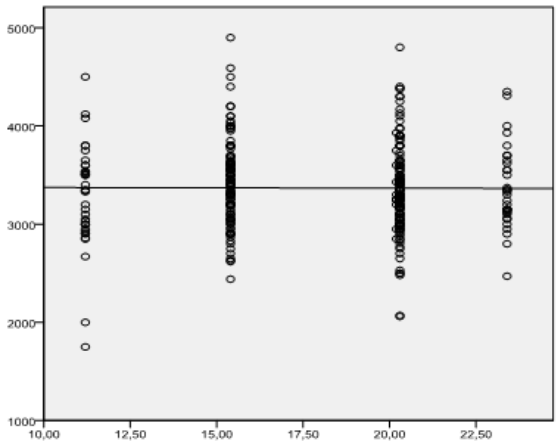


Figure 2: The correlation between total cLMWPTP activity (X axis) and BW (Y axis) in smoking (p=0.013) and in non smoking mothers (p=0.927)

Table 3 shows the relationship between maternal age and the effect of maternal cLMWPTP activity on BW in smoking and in non-smoking mothers. The median of maternal age is 28 years. Maternal age is grouped into two classes: ≤ 28 years and > 28 years and cLMWPTP activity is grouped into two classes: low and medium-high activity. The effect of maternal cLMWPTP on the relationship between smoking and BW is present in mothers aging more than 28 years but it is absent in smoking mothers aging 28 years or less.

	Low cLMWPTP activity (maternal)			Medium-high cLMWPTP activity (maternal)			Significance of differences
	Mean BW(grams)	S.E.	N°	Mean BW(grams)	S.E.	N°	
Smoking Mothers							
Maternal age ≤ 28 yrs	3333	237	7	3483	105	12	P=0.513
Maternal age >28 yrs	2853	146	7	3402	209	5	P=0.04
Non-smoking Mothers							
Maternal age ≤ 28 yrs	3359	44	98	3339	37	113	P=0.727
Maternal age >28 yrs	3415	70	46	3398	68	53	P=0.863

Table 3: Maternal age and the effect of maternal cLMWPTP on BW in smoking and non-smoking mothers. 28 years is the median of maternal age. P is the probability value (t- test) for the difference of BW between low vs medium-high cLMWPTP activity

Considering the whole sample of newborns, no statistically significant association between maternal age and BW has been observed.

A variance analysis with dependent BW has shown a statistically significant interaction of smoking with maternal age (p=0.05) and with cLMWPTP (p=0.03).

Discussion: The present analysis suggests that fetal cLMWPTP also exerts a modulating action on the effect of cigarette smoking upon BW: newborns with low cLMWPTP activity from smoking mothers have a higher risk of low BW as compared to newborns with medium-high cLMWPTP activity. Moreover, the analysis shows a significant effect of maternal age: the modulating action of maternal ACP_1 genotype on the relationship between smoking and BW is present in mothers aging more than 28 years only.

cLMWTP shows a large spectrum of activities on metabolic and immunological functions. The effects observed could be related to interactions between toxic substances of cigarette smoking and cLMWPTP: low enzymatic activity could be less efficient in the detoxification of damaging substances from cigarette smoking. On the other hand, these substances could contribute to inactivate cLMWPTP resulting in negative metabolic and immunological effects depending on ACP1 genotype. In this context it is interesting that: (i) reactive oxygen species are involved in the pathological manifestation associated to cigarette smoking [9-11]; (ii) F isoform is much less stable under the action of oxidative substances as compared to S isoform [7,8] and (iii) in smoking mothers there is a statistically significant positive correlation of BW with F isoform concentration but not with S isoform Table 2. Thus cigarette smoking could contribute to decrease BW through a prevalent inactivation of F isoform.

The role of maternal age represents an important observation emerging from the analysis. With advancing age smoking women could experience a cumulative effect of toxic substances from cigarette smoking that progressively aggravates the effect on intrauterine development resulting in a more evident effect of cLMWPTP upon clinical manifestation. Low enzymatic activity is associated through the action of ZAP70 to a decrease of T cell receptor signaling: a further decrease of cLMWPTP activity due to cigarette smoking could influence the feto-maternal immunological relationship with negative effects on fetal growth. In this context it is interesting the observation that chronic administration of nicotine to rats causes T cell anergy [12].

The interaction between cLMWPTP and cigarette smoking on BW could be an example of a more general phenomenon. The action of toxic environmental substances could be significantly modulated by the activity of cLMWPTP with important effects on the risk of over clinical manifestations. Older women with low cLMWPTP enzymatic activity should be informed that cigarette smoking is associated to high risk of low birth weight.

References:

1. Bottini E, Gloria-Bottini F, La Torre M, Lucarini N (2001) The genetics of signal transduction and the effect of smoking on intrauterine growth. Int J Epidemiol 30: 400-402.
2. Spencer N, Hopkinson DA, Harris H (1964) Quantitative differences and gene dosage in the human red cell acid phosphatase polymorphism. Nature 201: 299-300.
3. Bottini E, Gloria-Bottini F, Borgiani P (1995) ACP1 and human adaptability. 1. Association with common diseases: a case-control study. Hum Genet 96: 629-637.
4. Bottini N, Bottini E, Gloria-Bottini F, Mustelin T (2002) Low-molecular-weight protein tyrosine phosphatase and human disease: in search of biochemical mechanisms. Arch Immunol Ther Exp (Warsz) 50: 95-104.
5. Bottini N, Stefanini L, Williams S, Alonso A, Jascur T, et al. (2002) Activation of ZAP-70 through specific dephosphorylation at the inhibitory Tyr-292 by the low molecular weight phosphotyrosine phosphatase (LMPTP). J Biol Chem 277: 24220-24224.
6. Alho I, Costa L, Bicho M, Coeiho C (2013) The role of low molecular weight protein tyrosine phosphatase (LMWPTP ACP1) in oncogenesis. Tumour Biol 34: 1979-1989.
7. Bottini E, Modiano G (1964) Effect of oxidized glutathione on human red cell acid phosphatases. Biochem Biophys Res Commun 17: 260-264.
8. Bottini E, Modiano G, Santolamazza C, Filippi G, Businco L (1971) Studies of the in vitro effects of oxidized glutathione and acetylphenylhydrazine on acid phosphatases of human red blood cells. An experimental model for the investigation of hemolytic drug action at the molecular level. Clin Chim Acta 31: 243-254.
9. Saetzler RK, Arfors KE, Tuma RF, Vasthare U, Ma L, et al. (1999) Polynitroxylated hemoglobin-based oxygen carrier: inhibition of free radical-induced microcirculatory dysfunction. Free Radic Biol Med 27: 1-6.

10. Anderson C, Majeste A, Hanus J, Wang S (2016) E-Cigarette Aerosol Exposure Induces Reactive Oxygen Species, DNA Damage, and Cell Death in Vascular Endothelial Cells. Toxicol Sci 154: 332-340.
11. Calderón-Garcidueñas L (2016) Smoking and Cerebral Oxidative Stress and Air Pollution: A Dreadful Equation with Particulate Matter Involved and One More Powerful Reason Not to Smoke Anything! J Alzheimers Dis 54: 109-112.
12. Singh SP, Kalra R, Puttfarcken P, Kozak A, Tesfaigzi J, et al. (2000) Acute and chronic nicotine exposures modulate the immune system through different pathways. Toxicol Appl Pharmacol 164: 65-72.