Evaluation of association of DRD2 TaqIA and -141C InsDel polymorphisms with food intake and anthropometric data in children at the first stages of development

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Abstract

The reward sensation after food intake may be different between individuals and variants in genes related to the dopaminergic system may indicate a different response in people exposed to the same environmental factors. This study investigated the association of TaqIA (rs1800497) and -141C InsDel (rs1799732) variants in DRD2/ANKK1 gene with food intake and adiposity parameters in a cohort of children. The sample consisted of 270 children followed until 7 to 8 years old. DNA was extracted from blood and polymorphisms were detected by PCR-RFLP analysis. Food intake and nutritional status were compared among individuals with different SNP genotypes. Children carrying the A1 allele (TaqIA) had higher energy of lipid dense foods (LDF) when compared with A2/A2 homozygous children at 7 to 8 years old (GLMp=0.004; Mann Whitney p=0.005). No association was detected with -141C Ins/Delpolymorphism. To our knowledge, this is the first association study of the DRD2 TaqIA and -141C Ins/Del polymorphism with food intake and anthropometric parameters in children. DRD2 TaqIA polymorphism has been associated with a reduction in D2 dopamine receptor availability. Therefore, the differences observed in LDF intake in our sample may occur as an effort to compensate the hypodopaminergic functioning.

Keywords: Child obesity, DRD2 polymorphisms, food intake.

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Introduction

The prevalence of childhood overweight and obesity had a dramatic increase between 1990 and 2010, rising from 4.2% to 6.7%, and it is estimated that in 2020 the rate will be 9.1%, or approximately 60 million children (de Onis et al., 2010). The obesity prevalence in developed countries is twice higher than in developing countries. However, most of the affected children (35 million) live in developing countries (de Onis et al., 2010). Moreover, the relative increase rate of obesity in recent decades was higher in developing countries (+65%) than in developed countries (+48%) (de Onis et al., 2010; Oggioni et al., 2014). Obese children are more likely to become obese adults, and have higher risk of developing coronary heart diseases and other related diseases, which diminish life expectancy (Must, 1996; Rossner, 1998; Berenson, 2012). Insulin resistance, metabolic syndrome, and type 2 diabetes are also consequences of childhood obesity (Gupta et al., 2012).

Some factors contribute to overweight and obesity, such as low physical activity, high intake of high fat and sugar foods, change from the rural lifestyle to the urban, sociocultural factors, age, gender, and genetic factors (Popkin, 2006; Gupta et al., 2012; Oggioni et al., 2014). The sensation of reward after food intake, especially of palatable foods, may be different among individuals and might cause different amounts of food ingestion (Berridge et al., 2010). The dopaminergic system regulates food intake through a reward system, and although its function in eating disorders is poorly understood, it is known that the use of dopamine D2 receptor agonists decreases food intake in rats (Terry et al., 1995). A study that analyzed images via...
Positron Emission Tomography (PET) scans shows that obese individuals have low concentration of striatal D2 dopamine receptors as a mechanism of downregulation due to high levels of dopamine, indicating that the reduction of these receptors could be associated with an addictive behavior also observed in drug users (Wang et al., 2001). DRD2/ANKK1 gene polymorphisms alter the density of dopamine receptors, and thus may explain the different food intake levels in individuals exposed to the same environmental factors (Stelzel et al., 2010).

Several studies have associated the TaqIA (rs1800497) polymorphism with obesity, body mass index (BMI), and food intake (Barnard et al., 2009; Winkler et al., 2012; Cameron et al., 2013; Carpenter et al., 2013). However, to our knowledge, there is no study linking the -141C Ins/Del (rs1799732) polymorphism to obesity, although it was associated with other pathologies such as alcoholism and schizophrenia (Jonsson et al., 1999a; Johann et al., 2005; Lafuente et al., 2008a,b). Therefore, the objective of the present study was to analyze the association of TaqIA and -141C Ins/Del polymorphisms with adiposity parameters and food intake of children.

Materials and Methods

Subjects

The sample consisted of 270 children followed until 7 to 8 years old on average. The nutritional and anthropometric data were collected at 12 to 16 months, 3 to 4 and 7 to 8 years. The children included in the present study participated in a randomized controlled trial of dietary counseling on breast feeding and diet during the first year of life. The trial consisted of 500 children, randomized in a control or intervention group, of which mothers received a dietary advice about breastfeeding and complementary feeding during home visits in children’s first year of life. This dietary advice was based on the “Ten steps to Healthy Feeding”, a Brazilian national health policy for primary care, supported by World Health Organization (2006). More information of the first phase of the study can be found elsewhere (Vitolo et al., 2010), but in Table 1 we described the main characteristics of the sample. A substantial reduction of the sample occurred throughout the study and the main reason for the losses was the inability to locate the participants’ homes, usually due to the family moving to another city. Other reasons for losses were refusal to continue and children or maternal death. This intervention was not the primary objective of the present research and the participation in the intervention or control group was used as a confounding factor in statistical analyses.

Ethnicity was defined by the interviewer by skin color (i.e., whites and non-whites). More details of the traits studied are described elsewhere (Galvão, 2012; Louzada et al., 2012; Fontana et al., 2015; Miranda et al., 2015). This study was conducted according to the guidelines of the

| Characteristics                              |            |
|----------------------------------------------|------------|
| Ethnicity (whites)                          | 210 (77.8) |
| Sex (boys)                                  | 149 (55.2) |
| **12 to 16 months**                         |            |
| Child’s BMI (Z-score)                       | 0.59 ± 1.07|
| Average daily energy intake (kcal)          | 948.51 ± 398.56 |
| **3 to 4 years**                            |            |
| Child’s BMI (Z-score)                       | 0.27 ± 1.16 |
| Average daily energy intake (kcal)          | 1520.21 ± 391.36 |
| Sugar dense food intake (SDF; kcal)         | 105.94 ± 86.15 |
| Lipid dense food intake (LDF; kcal)         | 177.18 ± 190.81 |
| Average daily energy intake per kilogram (kcal/kg) | 91.23 ± 27.27 |
| **7 to 8 years**                            |            |
| Child’s BMI (Z-score)                       | 0.41 ± 1.38 |
| Average daily energy intake (kcal)          | 1564.54 ± 381.34 |
| Sugar dense food intake (SDF; kcal)         | 230.02 ± 194.97 |
| Lipid dense food intake (LDF; kcal)         | 85.10 ± 80.33 |
| Average daily energy intake per kilogram (kcal/kg) | 59.75 ± 18.10 |

aData are presented as % (n).
bData are presented as mean ± standard deviation.

Table 1 - Main characteristics of the sample.

Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Universidade Federal de Ciências da Saúde de Porto Alegre (n. 286/06), and all participants provided written informed consent before commencing the study.

Nutritional status assessment

At 12 to 26 months, children were weighted using a portable digital scale (Techline, São Paulo, Brazil) and length was measured by an infant stadiometer (Serwital Inc, Porto Alegre, Brazil). At 3 to 4 and 7 to 8 years, children were weighted using a digital scale (Techline), and height was measured using a stadiometer (SECA, Hamburg, Germany). BMI was calculated [weight (kg)/height²(m²)], and the values were transformed into Z-scores.

Dietary data assessment

One 24-hour dietary recall was collected for each child at 12 to 16 months, and two 24-hour dietary recalls, on two nonconsecutive days, were collected for each child at the ages of 3 to 4 and 7 to 8 years. The 24-hour dietary recall was carried out by a trained undergraduate nutrition student, and the child’s food intake was recorded on the day before the last home visit. A food portion measurement device and the common household measures (e.g. teaspoons, tablespoons, cups) were used to quantify portion sizes.
Dietary information was entered into the Nutrition Support Program software from the Escola Paulista de Medicina, Federal University of São Paulo, based on the United States Department of Agriculture chemical composition tables. The energy intake was calculated using only one dietary recall or the average of two dietary recalls. The items listed in the response were classified as sugar-dense foods (SDF) if the percentage of simple carbohydrates was higher than 50% (e.g., soda, Jell-O, candies, and artificially flavored juice) and as lipid-dense foods (LDF) if there was more than 30% fat (e.g., fried pastries, cookies with fillings, cold cuts and sausages, fried foods, and chocolate).

DNA analyses

Blood samples for DNA extraction were collected in EDTA tubes (6 mL). Genomic DNA was extracted from peripheral blood leukocytes by the Lahiri and Nurnberger procedure (Lahiri and Nurnberger, 1991). DRD2/ANKK1 TaqIA (rs1800497) and -141C InsDel (rs1799732) polymorphisms were detected by PCR-RFLP analysis using primer sequences and conditions described by Grandy et al. (1993) and Ohara et al. (1998), respectively. Primers sequences (IDT Coralville, IA, USA) were as follows: TaqIA, forward primer 5’- CACCTTCTGAGTGTACAA -3’ and reverse primer 5’- AGACAACCTGGCCAG CCGTG-3’; -141C InsDel, forward primer 5’- ACTGTCG GACGAGCGTGGAG and reverse primer 5’- TGCCGCGTGAGGCTGCGGT. PCR products were digested separately with either TaqI (TaqIA polymorphism) or MvaI (-141C InsDel polymorphism) enzyme (Fermentas, Glen Burnie, MD, USA), according to the manufacturer’s instructions. Genotypes were determined after electrophoresis in 2 or 3% agarose gels that had been stained with ethidium bromide. For the DRD2/ANKK1 TaqIA polymorphism, the C allele contains a TaqI restriction site and is designated as the A2 allele, while the T allele is designated as the A1 allele. For the -141C InsDel polymorphism, the -141C*Ins allele contains a restriction site for MvaI while the -141C*Del allele does not.

Statistical analyses

Allele frequencies were estimated by gene counting. A chi-square test for goodness-of-fit was used to determine whether the observed genotype frequency distributions agreed with those expected under Hardy-Weinberg equilibrium. Linkage disequilibrium was estimated using the Haploview software Version 4.2 (Broad Institute, Barrett et al., 2005).

Pearson’s chi-squared or Fisher’s Exact Test was used to compare genotype or allele frequencies between white and non-white children. Since the first publication of an association study with the TaqIA polymorphism (Blum et al., 1990), and because of the rare occurrence of the A1 allele, genotypes are normally grouped as A1 allele presence or A1 allele carriers (A1/A1 and A1/A2, n=102), versus A2/A2 homozygotes (n=116). Similarly, due to low frequencies of the Del allele, genotypes of the -141C InsDel polymorphism were grouped by Del allele presence or Del allele carriers (Del/Del and Ins/Ins, n=61), versus Ins/Ins homozygotes (n=157). All data are presented as mean and standard deviation. Statistical analysis of SDF and LDF variables were performed on natural logarithm transformed data to normalize their distribution. This allowed including these variables in multivariate analysis; non-transformed values are shown in Table 2. Means of food intake (average daily energy intake, SDF, LDF and average daily energy intake per kilogram) and adiposity (BMI Z-score) parameters were compared among genotype groups by a multivariate general linear model (GLM). The multivariate GLM was performed including all dependent continuous variables in one model, using the categorical variables (1) the control or intervention variable of the randomized trial, (2) sex, and (3) ethnicity as covariates, and genotypes of -141C InsDel (rs1799732) and TaqIA (rs1800497) polymorphisms as fixed factors (see Table 2). This first step of the analysis verified whether the group of dependent continuous variables was significantly affected by the group of independent categorical variables. Only LDF intake at 7 to 8 years old was associated with TaqIA polymorphism, and the covariates did not influence this dependent variable. Therefore, to test the association of TaqIA polymorphism alone with LDF intake at 7 to 8 years, we performed a Mann-Whitney test. A p-value of < 0.05 was considered significant. All tests and transformations were performed using the Statistical Package for Social Sciences, Version 20.0 (SPSS®, Chicago, IL, USA).

Results

This longitudinal survey sample was composed of 270 children, 149 (55.2%) boys and 121 (44.8%) girls, followed up from 12 to 16 months until 7 to 8 years old (Table 1). Minor allele frequencies (MAF) of the DRD2/ANKK1 gene variants observed in the sample were 0.14 of Del allele of the -141C InsDel (rs1799732) polymorphism and 0.28 of A1 allele of the TaqIA (rs1800497) polymorphism, which were intermediary to those described in the 1000 Genomes Project database for European (MAF 0.08 (Del) and 0.19 (A1)) and African (MAF 0.57 (Del) and 0.38 (A1)) populations. All genotype frequencies in this sample were in agreement with those expected under the Hardy-Weinberg equilibrium. The two gene variants were not in linkage disequilibrium (D'=0.3, r=0).

In Table 2, anthropometric and food intake variables are shown according to the analyzed polymorphisms. As some children could not be found at the third home visit at 7 to 8 years, and some samples could not be analyzed in the laboratory, the total number of children included in the multivariate analysis is different from the initial sample size. Children carrying the A1 allele (TaqIA rs1800497) had higher energy of LDF when compared with A2/A2 ho-
mozygous children at 7 to 8 years old (multivariate GLM \( p=0.004 \); Mann-Whitney test \( p=0.005 \)). No association was detected among DRD2 -141C Ins/Del polymorphism with food intake and anthropometric parameters.

### Discussion

The dopaminergic pathway has been associated with midbrain reward circuit activation (Roth et al., 2013), and individual differences in D2 receptor expression are hypothesized to contribute to differences in motivated behaviors, such as the motivation to eat (Gluskin and Mickey, 2016). Therefore, polymorphisms of the ANKK1/DRD2 gene are frequently associated with altered perception of food reward and weight gain (Ariza et al., 2012; Muller et al., 2012; Roth et al., 2013). TaqIA is the most commonly tested polymorphism, and is characterized by a single nucleotide change [C(A2)/T(A1)] located downstream of the termination codon of DRD2 gene at the ankyrin repeat and kinase domain containing 1 (ANKK1) gene (Dubertret et al., 2004; Neville et al., 2004; Li et al., 2015; Ponce et al., 2016). This SNP produces a Glu713-to-Lys (E713K) substitution in the ANKK1 amino acid sequence, at the eleventh ankyrin, which may alter the affinity of the ANKK1 protein and its substrate (Neville et al., 2004). It is not clear by which molecular mechanisms the ANKK1 protein could be associated with the dopaminergic system and how ANKK1 polymorphic alleles would impact addiction vulnerability. However, ANKK1 and DRD2 genes belong to the same gene cluster, the NTAD cluster, an ancient cluster of which genes are apparently co-regulated and may be the same gene cluster, the NTAD cluster, an ancient cluster of which genes are apparently co-regulated and may have emerged when the central nervous system became more complex (Mota et al., 2012). Since genes of related function are sometimes found in the same cluster, it is possible that ANKK1 is somehow involved in the dopaminergic reward processes via a signal transduction pathway (or other cellular response) (Neville et al., 2004). A few in vitro studies with ANKK1 gene mRNAs and proteins were able to show a potential connection between this gene and the dopaminergic system (Hoenicka et al., 2007; Garrido et al., 2011).

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**Table 2** - Food intake and anthropometrics parameters according to polymorphisms in DRD2/ANKK1 gene (-141C Ins/Del and TaqIA) in children at 1, 3 to 4, and 7 to 8 years old.

| Genotypes | Ins/Ins \( n=157 \) | Del carriers \( n=61 \) | \( p \) | A1 carriers \( n=102 \) | A2A2 \( n=116 \) | \( p \) |
|-----------|----------------|----------------|-----|----------------|----------------|-----|
| 12 to 16 months | | | | | | |
| Average daily energy intake (kcal) | 930.95 ± 400.09 | 957.32 ± 390.89 | 0.601 | 917.78 ± 395.82 | 956.66 ± 398.51 | 0.845 |
| BMI Z-score | 0.60 ± 1.13 | 0.48 ± 1.04 | 0.609 | 0.52 ± 1.05 | 0.62 ± 1.15 | 0.436 |
| 3 to 4 years | | | | | | |
| Average daily energy intake (kcal) | 1506.24 ± 396.82 | 1579.95 ± 419.60 | 0.175 | 1476.62 ± 337.72 | 1571.04 ± 450.73 | 0.453 |
| SDF (kcal) | 112.00 ± 97.91 | 110.77 ± 77.42 | 0.969 | 110.0 ± 86.95 | 113.11 ± 97.40 | 0.623 |
| LDF (kcal) | 191.55 ± 197.10 | 162.20 ± 189.60 | 0.288 | 168.83 ± 179.06 | 196.09 ± 208.03 | 0.884 |
| BMI Z-score | 0.27 ± 0.96 | 0.28 ± 1.62 | 0.839 | 0.29 ± 1.17 | 0.25 ± 1.19 | 0.774 |
| Average daily energy intake per kilogram (kcal/kg) | 91.92 ± 27.74 | 94.84 ± 29.75 | 0.448 | 89.43 ± 24.96 | 95.65 ± 30.71 | 0.327 |
| 7 to 8 years | | | | | | |
| Average daily energy intake (kcal) | 1560.73 ± 355.60 | 1581.21 ± 414.36 | 0.756 | 1581.13 ± 354.41 | 1553.56 ± 388.07 | 0.481 |
| SDF (kcal) | 90.52 ± 75.95 | 68.03 ± 58.51 | 0.164 | 76.97 ± 62.02 | 90.60 ± 79.62 | 0.847 |
| LDF (kcal) | 238.38 ± 203.75 | 223.48 ± 181.94 | 0.782 | 282.85 ± 207.96 | 191.77 ± 178.34 | 0.004 |
| BMI Z-score | 0.45 ± 1.26 | 0.25 ± 1.65 | 0.514 | 0.50 ± 1.36 | 0.30 ± 1.40 | 0.258 |
| Average daily energy intake per kilogram (kcal/kg) | 59.99 ± 17.00 | 60.97 ± 20.91 | 0.861 | 59.83 ± 17.45 | 60.65 ± 18.78 | 0.739 |

Data are presented as mean ± standard deviation.

BMI – body mass index. SDF – sugar dense foods. LDF – lipid dense foods. General Linear Model (GLM) multivariates with the following co-variates: group (intervention or control), sex, ethnicity. Statistical analysis from logarithm form, non-transformed values are shown; Mann-Whitney test \( p=0.005 \).
In our sample, the A1 allele (TaqIA rs1800497) was found associated with higher intake of LDF when compared with children A2/A2 homozygous at 7 to 8 years. This allele has been associated with a reduction in D2 receptor availability (Pohjalainen et al., 1998; Ritchie and Noble, 2003; Eisenstein et al., 2016). Stice et al. (2008) found that the dorsal striatum is less responsive to food reward in obese relative to lean individuals, probably because obese individuals have reduced D2 receptor density that compromises dopamine signaling. This hypodopaminergic functioning or reward deficiency syndrome may induce obese patients to overeat in an effort to compensate for this reward deficit; several studies are consistent with this theory (van Strien et al., 2010; Duran-Gonzalez et al., 2011; Winkler et al., 2012; Cameron et al., 2013). van Strien et al. (2010) associated the A1 allele with an increase in emotional eating in Dutch adolescents. The A1 allele was also most frequent in young obese Mexican-American subjects than in non-obese, as well as subjects with central-obesity versus subjects with no central-obesity (Duran-Gonzalez et al., 2011). Winkler et al. (2012) observed in an intervention study that carriers of the A1 allele had a higher BMI at all time-points (baseline, after weight loss, and after weight maintenance), and showed less overall weight loss. Similarly, Cameron et al. (2013) observed that post-menopausal women carriers of the A1 allele lost significantly less body weight and fat mass than women with the A2/A2 genotype after undergoing an intervention-induced weight loss and increased carbohydrate intake. Some studies were not able to find any association of the DRD2 TaqIA polymorphism with adiposity parameters (Hardman et al., 2014).

In the present study, no association was detected between DRD2 -141C Ins/Del polymorphism with food intake and anthropometric parameters, despite previous findings relating Del carriers of the DRD2 -141C Ins/Del polymorphism with higher D2 receptor density (Jonsson et al., 1999b). The DRD2 -141C Ins/Del polymorphism corresponds to a deletion of one cytosine from a run of two cytosines at position -141 of the DRD2 gene (Arinami et al., 1997). This polymorphism has been associated with risk of schizophrenia in different populations (Arinami et al., 1997; Ohara et al., 1998; Jonsson et al., 1999a; Himei et al., 2002; Wu et al., 2005; Lafuente et al., 2008a,b; Cordeiro et al., 2009; Saiz et al., 2010; Xiao et al., 2013; Wang et al., 2016; Zhao et al., 2016), as well as with weight gain (Lencz et al., 2010) and other responses due to schizophrenia drug treatment (Lencz et al., 2006; Zhang et al., 2010). Associations have been described with propensity to alcohol dependence in different populations (Ishiguro et al., 1998; Konishi et al., 2004a,b; Johann et al., 2005; Du and Wan, 2009; Prasad et al., 2010; Lee et al., 2013), suicide attempts (Suda et al., 2009), psychiatric disorders (Kishida et al., 2004; Ujike et al., 2009; Lencer et al., 2014), different responses to medication and higher quit rates in smokers (Lerman et al., 2006). To the best of our knowledge, there is no other study that associated the DRD2 -141C Ins/Del polymorphism with anthropometric parameters or food intake.

The lack of associations in the two other phases of development (12 to 16 months and 3 to 4 years) may have occurred because children at these ages have restricted access to food, and depend on adults for meals, despite their own preferences. Notwithstanding, at 7 to 8 years, children have many opportunities to eat without parental supervision (Briefel et al., 2009), and the differences observed in LDF intake in our sample may have occurred as an effort to compensate hypodopaminergic functioning.

Palatability is the induced sensitive response of foods that are usually rich in lipids and/or sugar (Cansell and Luquet, 2016). The sense of taste during food ingestion is the most important aspect in the decision to consume or avoid foods (Bensard, 2016). Contrary to sugar, oral fat perception was considered dependent only on its textural and olfactory cues, but recent identification of lipid-receptors in taste buds of both rodents and humans strongly suggests that lipids might also be perceived by the gustatory pathway (Bensard, 2016). Stimulation of taste buds triggers a signaling cascade leading to subsequent neurotransmitter releases in different brain areas responsible for taste perception (e.g., anterior insula, frontal operculum, orbitofrontal cortex, and the mesolimbic system) (Bensard, 2016). The exchange between these areas results in information of the hedonic experience related to the food’s taste (Berridge, 1996). Therefore, not only sugar, but also lipids generate a hedonic experience, producing a positive reinforcement that stimulates dopamine secretion in the brain (Salamone, 1994, Volkow et al., 2002), which is a stimulus associated with “wanting” (Berridge et al., 2010). “Wanting” is an incentive salience or motivation for reward triggered by reward-related cues, such as LDF (Berridge et al., 2010). The attribution of incentive salience makes a cue and its reward more attractive, or more “wanted”, without being necessarily more “liked” (Berridge et al., 2010). Consistent with our findings, other studies of our group detected associations of palatable food intake with another polymorphism related to the dopaminergic system in children of the same cohort at 12 to 16 months and 3 to 4 years old (Galvão et al., 2012; Fontana et al., 2015). However, further research is needed to confirm the association of DRD2 TaqIA polymorphism with LDF intake and its potential mechanisms.

In summary, our results showed that TaqIA polymorphism may have an influence on the children’s eating behavior, due to the presence of the A1 allele associated with lower D2 receptor density that may lead children to compensate the hypodopaminergic functioning with palatable foods. To our knowledge, this is the first association study of the DRD2 TaqIA and -141C Ins/Del polymorphism with food intake and anthropometric parameters in children at the first stages of development. Notwithstanding, it is nec-
ecessary to replicate this findings in other populations and identify the mechanisms by which the dopaminergic system may influence food intake. Nevertheless, the investigation of other polymorphisms in this and other genes of the dopaminergic system and their relation to food intake and anthropometric parameters may be interesting.

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