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TESE DE DOUTORADO

EFEITO DA RESISTÊNCIA À INSULINA EM PROCESSOS COGNITIVOS RELACIONADOS AO COMPORTAMENTO ALIMENTAR DE INDIVÍDUOS COM BAIXO PESO AO NASCER: EVIDÊNCIAS DO CICLO VICIOSO DA OBESIDADE

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Co-orientadora: Patrícia Pelufo Silveira

Porto Alegre, 2018

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Ao Giovanni e aos meus filhos,

sentido da minha vida.

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Orandum est ut sit mens sana in corpore sano.	Deve-se pedir em oração que a mente seja sã num corpo são.
fortem posce animum mortis terrore carentem,	Peça uma alma corajosa que careça do temor da morte,
qui spatium uitae extremum inter munera ponat	que ponha a longevidade em último lugar entre as bênçãos da natureza,
naturae, qui ferre queat quoscumque labores,	que suporte qualquer tipo de labores,
nesciat irasci, cupiat nihil et potiores	desconheça a ira, nada cobice e creia mais
Herculis aerumnas credat saeuosque labores	nos labores selvagens de Hércules do que
et uenere et cenis et pluma Sardanapalli.	nas satisfações, nos banquetes e camas de plumas de um rei oriental.
monstro quod ipse tibi possis dare; semita	Revelarei aquilo que podes dar a ti próprio;
Certe tranquillae per uirtutem patet unica uitae.	Certamente, o único caminho de uma vida tranquila passa pela virtude.

(Juvenal, 10.356-64)

Resumo

A programação do metabolismo e do comportamento alimentar e a posterior exposição a alimentos hiperpalatáveis possivelmente expliquem o risco aumentado para doenças crônicas relacionadas à obesidade dos indivíduos com baixo peso ao nascer. Especificamente, as evidências indicam que essa população é mais propensa à resistência à insulina e ao dano hipocampal e que a associação de ambos pode explicar, em parte, a disfunção no controle alimentar e na saúde metabólica. Os indivíduos com restrição fetal do crescimento, portanto, seriam mais propensos ao ciclo vicioso da obesidade: desde a infância, são mais sensíveis à insulina e preferem alimentos hiperpalatáveis aos saudáveis; a maior ingestão desses alimentos induz progressivamente à resistência à insulina; a alteração na sinalização de insulina hipocampal prejudica a formação da memória alimentar e o controle inibitório frente a pistas alimentares; o maior consumo crônico de alimentos hiperpalatáveis rompe o equilíbrio e, consequentemente, surgem as doenças metabólicas relacionadas à obesidade na vida adulta. A proposta deste trabalho foi introduzir a hipótese do ciclo vicioso da obesidade em indivíduos nascidos com baixo peso, investigando, através de um delineamento translacional, se a resistência à insulina estaria associada ao processamento cognitivo diferencial frente às pistas alimentares nos indivíduos nascidos pequenos para a idade gestacional. (a) Primeiramente, verificou-se o ciclo vicioso da obesidade em um estudo com adolescentes saudáveis, representantes de todo o espectro de peso ao nascer, analisando se a resistência à insulina periférica estaria associada ao comprometimento da memória alimentar implícita e à desativação de áreas cerebrais associadas ao controle inibitório em resposta a imagens de alimentos hiperpalatáveis. (b) Após, verificou-se se o baixo peso ao nascer estaria associado a um comportamento alimentar obesogênico e à alteração do tamanho hipocampal e da sensibilidade à insulina em adolescentes. (c) Por fim, em um modelo de desnutrição gestacional em roedores, analisou-se se o baixo peso ao nascer modifica o estado metabólico, o comportamento alimentar e a função insulínica hipocampal, e se o consumo de alimentos hiperpalatáveis incrementaria essas mudanças. Uma carta ao editor e um artigo de revisão foram escritos com base nessas premissas. No estudo clinico, foi encontrada que a maior resistência à insulina está associada ao comprometimento da memória alimentar implícita e que quanto maior a resistência à insulina, maior ativação de áreas cerebrais associadas à atenção e menor ativação das associadas ao controle inibitório frente a imagens de alimentos hiperpalatáveis. Esse estudo também mostrou que o baixo peso ao nascer está associado a uma

ingestão mais densamente calórica, ao comprometimento da memória alimentar implícita, à redução do volume do subículo hipocampal e que a resistência à insulina interage com o peso ao nascer ao modular a ingestão alimentar externa. Por fim, o estudo experimental evidenciou que o baixo peso ao nascer está associado ao aumento da fosforilação do receptor glutamatérgico hipocampal induzido por insulina, à resistência à insulina hipocampal e à menor ingestão e entropia do comportamento alimentar quando há mudança na previsibilidade alimentar. Além disso, o baixo peso ao nascer junto à ingestão crônica de dieta hiperpalatável está associado ao maior ganho de peso corporal e ao reconhecimento da novidade alimentar. Ao reunir essas evidências, esta tese aponta que a associação da resistência à insulina ao comprometimento hipocampal explica, em parte, a alteração do comportamento alimentar dos indivíduos nascidos com baixo peso. Em um ambiente repleto de pistas alimentares, a ruptura do controle cognitivo pode levar ao ganho de peso e comprometer a saúde metabólica desses sujeitos ao longo do tempo.

Palavras-chave: Retardo do Crescimento Intrauterino. Comportamento Alimentar. Hipocampo. Síndrome X Metabólica. Resistência à Insulina. Pesquisa Médica Translacional.

Abstract

Metabolic and feeding behavioral programming with subsequent exposure to hyperpalatable foods can possibly explain the increased risk for chronic diseases related to obesity in individuals with low birth weight. Evidence indicate that this population is more prone to insulin resistance and hippocampal damage and that their association may partly explain the dysfunction in feeding control and metabolic health. Individuals with fetal growth restriction, therefore, would be more prone to the vicious cycle of obesity, they are more sensitive to insulin and prefer to eat hyperpalatable foods over more healthy options since childhood; the increased intake of these foods progressively induces insulin resistance; the alteration in hippocampal insulin signaling impairs the formation of food memory and the inhibitory control towards food cues; the greater chronic consumption of hyperpalatable foods disrupts the balance, and consequently, metabolic diseases related to obesity appear in adult life. The purpose of this study was to introduce the hypothesis of the vicious cycle of obesity in low birth weight individuals, investigating, through a translational design, whether insulin resistance would be associated with differential cognitive processing of foods cues in individuals born small for gestational age. (a) First, the vicious cycle of obesity was verified in a study with healthy adolescents from the full birth weight spectrum, analyzing whether peripheral insulin resistance would be associated with eating memory compromising and deactivation of brain areas associated with inhibitory control in response to hyperpalatable foods pictures. (b) Afterwards, it was verified whether low birth weight would be associated with an obesogenic eating behavior and with changes in hippocampal size and insulin sensitivity in adolescents. (c) Finally, in a model of gestational malnutrition in rodents, it was analyzed whether low birth weight modifies metabolic status, eating behavior and hippocampal insulin function, and whether the consumption of hyperpalatable foods would exacerbate these changes. A letter to the editor and a review manuscript were written based on these assumptions. In the clinical study, it was found that higher insulin resistance is associated with inconsistencies in implicitly learned food preferences and that the greater the insulin resistance, the greater activation of brain areas associated with attention and the lower activation of those associated with inhibitory control facing hyperpalatable foods pictures. This study also showed that low birth weight is associated with higher caloric intake, inconsistencies in implicitly learned food preferences, reduced hippocampal subiculum volume, and that insulin resistance interacts with birth weight by modulating food intake. Finally, the experimental study showed that low birth

weight is associated with increased phosphorylation of the hippocampal glutamatergic receptor induced by insulin, hippocampal insulin resistance and lower intake and feeding behavior entropy when there is a change in food predictability. In addition, low birth weight along with chronic intake of hyperpalatable diet is associated with greater body weight gain and the recognition of novel foods. In gathering this evidence, this thesis points out that the association between insulin resistance and changes in hippocampus partly explains the altered eating behavior of low birth weight subjects. In an environment full of food cues, the disruption in cognitive control may lead to weight gain and compromise the metabolic health of these subjects over time.

Key-words: Fetal Growth Retardation. Feeding Behavior. Hippocampus. Metabolic Syndrome X. Insulin Resistance. Translational Medical Research.

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LISTA DE ABREVIATURAS E SIGLAS

Adlib	*Ad libitum* control chow feeding
Adlib-CON	Offspring from Adlib dams fed with CON
Adlib-HFS	Offspring from Adlib dams fed with HFS
AGA	Adequate for gestational age
Akt	Protein kinase-B
ANOVA	Analysis of variance test
BioDAQ®	Food intake monitoring system, Research Diets®
BMI	Body mass index
CA	*Cornu ammonis*
CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
CNPq	Conselho Nacional de Desenvolvimento Científico e Tecnológico
CNS	Central nervous system
COM	Control diet
CV	Coefficients of variation
DEBQ	Dutch eating behaviour questionnaire
DOHaD	Developmental Origins of Health and Disease
FEW	Family-wise error
FIPE	Fundo de Investimento em Pesquisa e Eventos
FR	Restricted control chow feeding during gestation
FR-CON	Offspring from FR dams fed with CON
FR-HFS	Offspring from FR dams fed with HFS
GluN2A ou NR2A, GluN2B ou NR2B	NMDAR subunits
GLUT	Glucose transporter
HCPA	Hospital de Clínicas de Porto Alegre
HFS	High-fat and sugar or hyperpalatable diet
HOMA-IR	Homeostasis assessment model-insulin resistance
IP	Intraperitoneally
IQ	Inteligence quotient
IR	Insulin receptor

IUGR	Intrauterine growth restriction
MAPK	Mitogen-activated protein kinase
MRI	Magnetic resonance imaging
NAcc	Nucleus accumbens
NMDA ou NMDAR	Glutamatergic N-Methyl-D-Aspartate receptor
PFC	Pre-frontal cortex
PI3K	Phosphatidylinositol 3 kinase
PND	Postnatal day
PSD	Post-synaptic density
RCIU	Restrição do crescimento intrauterino
RM	Repeated measures
SD	Standard deviation
SGA	Small for gestational age
SOCS-3	Suppressor of cytokine signaling 3
STZ	Streptozotocin
T2DM	Type II diabetes *mellitus*
VTA	Ventral tegmental area
WASI	Wescheler Abreviated Scale of Inteligence

SUMÁRIO

1. INTRODUÇÃO

Esta tese inicia com a exposição de um referencial teórico sobre o impacto do baixo peso ao nascer no metabolismo e no neurodesenvolvimento do indivíduo, com uma correspondência publicada na revista *The Lancet,* comentando o tema, seguido da hipótese de um mecanismo cerebral envolvido na programação do comportamento alimentar dos indivíduos que sofreram redução do crescimento fetal, com um artigo de revisão publicado na revista *Neuroscience & Biobehavioral Reviews* sobre o assunto. Posteriormente, apresentam-se dois artigos em versões pré-submissão em que foram apresentados e discutidos os resultados da hipótese testada em humanos e roedores. Por fim, reúne e conclui os achados, apontando possíveis perspectivas sobre o tema proposto.

1.1. O BAIXO PESO AO NASCER

A restrição do crescimento intrauterino (RCIU) é definida como o crescimento fetal inferior ao esperado pelo potencial inerente de uma criança. A melhora do cuidado médico perinatal ocorrido na metade do século passado foi a principal responsável pelo aumento da sobrevivência dos indivíduos nascidos com RCIU (1), cuja prevalência é estimada entre 10 e 15% dos recém-nascidos (2). No entanto, a incidência de tais casos varia de acordo com a população, a localização geográfica e as curvas de crescimento utilizadas como referência. A presença da RCIU na população está concentrada principalmente na Ásia, que representa quase 75% de todas as crianças afetadas por essa condição, seguida da África e América Latina, que representam 20% e 5% dos casos, respectivamente (3,4).

Para ser diagnosticada corretamente, é necessário o acompanhamento por ultrassonografia durante a gestação. Entretanto, é comum que o peso ao nascer seja a única informação disponível para o registro de dados clínicos e, assim, os bebês geralmente são classificados com RCIU quando nascem com peso menor ao décimo percentil do peso da população específico para sexo e idade gestacional (5–7). Essa classificação pode ser arbitrária, pois, dependendo dos padrões de crescimento estabelecidos, alguns indivíduos podem ser considerados *small for gestational age* (SGA) ou pequenos para a idade

gestacional, mas não com RCIU, porque seu peso ao nascer se encontra dentro do intervalo normal (igual ou maior ao décimo percentil). É importante reconhecer que o diagnóstico de verdadeiros indivíduos com RCIU é desafiador na prática clínica, já que tanto crianças nascidas com peso menor que o décimo percentil podem não apresentar patologias relacionadas ao baixo peso ao nascer, quanto crianças que nasceram com o peso adequado para a idade gestacional podem não ter alcançado seu crescimento intrínseco (8–10). Nesta tese, entretanto, como foram utilizados bancos de dados onde havia apenas o peso ao nascer e a idade gestacional como informações sobre o crescimento fetal, os termos RCIU, baixo peso ao nascer e pequeno para a idade gestacional foram utilizados indiferentemente.

A etiologia da RCIU pode ser materna, fetal, placentária e genética (11) e, na maioria dos casos, é o resultado de uma disfunção na perfusão placentária-fetal, levando a circulação fetal à hipóxia e à acidose (12). Uma má nutrição gestacional e o baixo peso pré-gestacional são os maiores determinantes para a restrição de crescimento fetal nos países em desenvolvimento, enquanto que nos países desenvolvidos o fator mais importante é o tabagismo, seguido de uma má nutrição gestacional (13).

A RCIU representa uma adaptação a um ambiente pré-natal adverso que gera processos compensatórios no feto, resultando num sobrevivente intacto, porém sob risco de desfechos mórbidos (14). Ela é caracterizada como simétrica se peso, comprimento e circunferência da cabeça são proporcionalmente menores que o padrão, ou assimétrica quando a circunferência da cabeça está dentro dos limites normais. A restrição assimétrica geralmente ocorre na fase hipertrófica ou tardia da gestação e é causada por um prejuízo na função uteroplacentária ou uma deficiência nutricional em que o crescimento fetal é normal até que a taxa de crescimento exceda o suprimento nutricional. Como consequência, a formação de glicogênio e gordura fetal é afetada, assim como o crescimento de músculos e ossos, a fim de redistribuir o débito cardíaco prioritariamente ao coração e ao cérebro (15).

No período perinatal, a RCIU aumenta as chances para mortalidade fetal e neonatal e para convulsões, hemorragia pulmonar, hipertensão pulmonar persistente, síndrome do desconforto respiratório, aspiração de mecônio, imunodeficiência, disfunção renal, paralisia cerebral, distúrbios hematológicos, hipotermia, hipoglicemia/hiperglicemia, hipocalcemia,

baixa ferritina sérica, policitemia/hiperviscosidade, enterocolite necrosante/intolerância alimentar, retinopatia de prematuridade, asfixia perinatal e infecções (11,16). Em longo prazo, as consequências da RCIU incluem o déficit de crescimento estatural, osteoporose, disfunção imunológica, doença reativa das vias aéreas, puberdade precoce, doenças renais e hepáticas, alguns tipos de câncer e menor vida útil, dentre outras implicações discutidas a seguir.

A programação metabólica na adversidade fetal

A RCIU pode ser vista como um período de fome fisiológica crônica, já que a escassez de recursos nutricionais durante a vida gestacional torna os indivíduos mais eficientes na aquisição e no estoque de energia (17–19). Essa estratégia é o resultado de mudanças estruturais e funcionais permanentes em órgãos responsáveis pela regulação nutricional e metabólica, como cérebro, fígado, tecido adiposo, músculo e pâncreas (20), levando, por exemplo, ao aumento da sensibilidade periférica à insulina para utilização da glicose, ao aumento da glicogênese hepática, à diminuição da sensibilidade à insulina para a síntese proteica nos músculos e ao comprometimento do desenvolvimento pancreático. De acordo com a hipótese do *thrifty phenotype* ou fenótipo poupador, essas adaptações favorecem a sobrevivência em curto prazo em um ambiente pós-natal pobre nutricionalmente (19), promovendo a melhor utilização da energia, reduzindo a demanda por aminoácidos e elevando a glicemia para manter o suprimento suficiente ao coração e ao cérebro.

Em contrapartida, conforme a hipótese *developmental origins of health and disease* (DOHaD) ou origens desenvolvimentistas da saúde e da doença, o ajuste funcional e estrutural predispõe o indivíduo a disfunções e doenças crônicas não transmissíveis na idade adulta (21,22). Para garantir a sobrevivência na adversidade, ocorre um crescimento assimétrico, com tecidos musculares e subcutâneos sofrendo a restrição mais pronunciadamente. Em condições de desnutrição pós-natal, essa adaptação leva os tecidos fetais a terem suas funções metabólicas basais dependentes da energia à custa do crescimento corporal (23). Entretanto, quando o suprimento nutricional aumenta, ocorre a absorção de energia além das necessidades e capacidades metabólicas, predispondo os

indivíduos pequenos para a idade gestacional à resistência à insulina, diabetes *mellitus* tipo II, adiposidade abdominal, doenças cardiovasculares e síndrome metabólica na idade adulta (24–29).

Além disso, o ambiente pós-natal do mundo moderno, com oferta excessiva de alimentos hiperpalatáveis, ricos em açúcar, gordura e/ou sal, densamente calóricos e pobres nutricionalmente, dispensa o consumo de alimentos *in natura* mais saudáveis e é um dos principais contribuintes para o desenvolvimento de doenças relacionadas à síndrome metabólica na população em geral – e mais ainda em indivíduos predispostos a elas, como os nascidos com RCIU (30,31). Baseada nisso, foi escrita uma correspondência à revista *The Lancet*, que se encontra no item 4.1. desta tese, salientando que os cuidados pré-gestacionais e pré-natais adequados são ainda a melhor estratégia para evitar as consequências da programação fetal na saúde em longo prazo (32).

A propensão à resistência à insulina

Um grande número de estudos epidemiológicos evidenciou a forte associação existente entre a RCIU e o subsequente desenvolvimento de diabetes *mellitus* tipo II na idade adulta (18,25,33,34). Os dados de modelos animais de RCIU induzido por desnutrição proteica sustentam esses achados (35,36) e indicam que essa associação seja mediada pelo *catch-up growth* ou crescimento de recuperação ocorrido no início da vida (37). Esse crescimento ocorre geralmente nos recém-nascidos com RCIU que receberam alimentação normal após o nascimento, levando a um ganho de massa gorda desproporcionalmente maior em comparação ao ganho de massa magra (38).

Sabe-se que a resistência à insulina e a disfunção das células-β das ilhotas pancreáticas são as duas principais características da diabetes *mellitus* tipo II (39,40). Em humanos predispostos a desenvolverem essa doença, como os com baixo peso ao nascer, o desequilíbrio na secreção e na ação da insulina pode ser detectado muito tempo antes da falência pancreática, mesmo que as células-β sejam capazes de secretar insulina suficientemente para compensar tanto o defeito no mecanismo de ação, quanto para manter a glicemia em níveis normais (definição de resistência à insulina). Contudo, a

sobrecarga das células-β induz a redução da secreção de insulina em níveis adequados, tendo como consequência a hiperglicemia.

Em seres humanos saudáveis, a elevação da glicemia induz o aumento da secreção de insulina e a proliferação de células-β (41,42), porém esse achado não é evidenciado em estudos com modelos animais de RCIU (43). Além disso, a proporção de células-β pancreáticas é diminuída nos fetos de roedores que sofreram restrição de crescimento, permanecendo reduzida durante todo o percurso da vida (35,36). Essa incapacidade de incrementar adequadamente a quantidade de células-β poderia ser decorrente tanto da menor proliferação celular, quanto da aumentada taxa de apoptose (44,45) e provavelmente possam ser consequência de modificações na regulação epigenética da expressão de genes implicados no metabolismo da glicose ocorrida durante a adversidade intrauterina (46–48), o que não parece ocorrem com as células-α e PP, responsáveis pela secreção pancreática de glucagon e somatostina (49,50).

Os efeitos da poupança cerebral ou *brain sparing*

A priorização da redistribuição do débito cardíaco ao cérebro na RCIU assimétrica é conhecida como poupança cerebral ou *brain sparing* (51), resultando em um índice de cefalização (circunferência da cabeça dividida pelo peso ao nascer) extremamente alto. Embora esse remanejamento tenha sido inicialmente considerado um mecanismo de proteção, ultimamente é considerado um indicador precoce de dano cerebral associado ao risco aumentado para alterações no neurodesenvolvimento (52–57). As implicações neurológicas da RCIU abrangem baixos escores em testes cognitivos, dificuldades escolares ou necessidade de educação especial, transtornos perceptivos, incluindo pior percepção visual-motora, menor escore de inteligência, disfunção motora fina e grossa e paralisia cerebral. Além disso, o baixo peso ao nascer está associado ao maior risco para transtornos psiquiátricos, como ansiedade, esquizofrenia, depressão e transtorno bipolar, baixa habilidade social e acadêmica e reduzida capacidade de trabalho, sendo que a incidência do comprometimento cognitivo grave é baixa, porém há um aumento na incidência de pequenos desvios cognitivos quando comparados com a população em geral (58–67).

Os mecanismos implicados na vulnerabilidade neurocomportamental da RCIU não são claros, mas as evidências sugerem que eles estejam associados a alterações na estrutura cerebral, com redução do volume intracraniano e da matéria cinzenta cortical (68). A RCIU também está associada a uma maturação anormal dos oligodendrócitos, resultando em uma reduzida mielinização e menor volume da matéria branca cerebral (69). Além disso, estudos em humanos e em modelos animais com RCIU mostraram que o hipocampo, reconhecido pelo papel em codificar, armazenar e evocar as informações relacionadas com aprendizagem e memória, é uma das áreas mais afetadas nessa condição. As subestruturas do hipocampo *Cornus Ammonis* (CA) 1, CA3 e giro denteado, além do subículo da formação hipocampal, são as regiões mais vulneráveis à hipóxia-isquemia, uma consequência inerente à insuficiência uteroplacentária (70). As principais mudanças estruturais sofridas pelo hipocampo na RCIU incluem redução no número de células e na matéria branca, além de alteração na composição celular e na morfologia dendrítica (71–73) Existem também evidências de modificações na expressão genética e proteica de fatores neurotróficos, de receptores glutamatérgicos e de proteínas da densidade pós-sináptica associadas ao baixo peso ao nascer, levando a mudanças da função sináptica hipocampal (74–77).

A neurobiologia do comportamento alimentar na restrição de crescimento fetal

O comportamento alimentar é moldado por elementos genéticos, fisiológicos, cognitivos, ambientais, psicossociais e culturais. Sua formação é iniciada desde a vida *in utero* (78,79) e os eventos que ocorrem durante o desenvolvimento fetal podem alterar permanentemente as vias cerebrais relacionadas ao consumo e ao gasto energético, comprometendo as preferências alimentares durante todo o percurso de vida (80–83).

Existem evidências de que os indivíduos com RCIU comem mais (84,85) e se exercitam menos (86–88), bem como também tem preferência específica para os alimentos hiperpalatáveis. Desde o primeiro dia da vida, é possível detectar diferenças na resposta hedônica ao sabor do doce de acordo com o grau de RCIU em recém-nascidos pré-termo e a termo (89–91). Durante a infância, é possível detectar maior impulsividade frente ao alimento doce (92) e maiores dificuldades alimentares em crianças nascidas pequenas para a

idade gestacional (93–96). Além disso, ao longo da vida, o baixo peso ao nascer está associado a uma programação das preferências alimentares, com o aumento do consumo de alimentos ricos em carboidratos e gordura, em comparação a frutas e vegetais (31,97–102). Estudos recentes têm também verificado um comportamento alimentar característico em modelos animais: ratos com RCIU comem mais alimentos hiperpalatáveis e apresentam alterações de comportamento em tarefas que utilizam estes alimentos como recompensa (103–106), sugerindo que estes animais com RCIU sejam mais orientados para a recompensa alimentar (104,105).

Evidências mostraram que a deficiência nutricional na vida precoce promove o aumento da ingestão alimentar e da ativação de neurônios rostrais e mediais do núcleo do trato solitário em resposta à estimulação por alimento na fase adulta, indicando que o tronco encefálico é uma região vulnerável às influências da manipulação nutricional nos estágios precoces de desenvolvimento, tendo efeitos no controle alimentar em longo-prazo (107). Além disso, existe associação da deficiência nutricional perinatal com uma menor saciedade em resposta à leptina e a uma sinalização prejudicada deste hormônio no núcleo arqueado (108–111), assim como maior resposta a sinais motivadores do apetite, como a grelina (112). A adversidade neonatal também está associada a uma expressão aumentada de neuropeptídeos orexígenos em comparação aos anorexígenos (113–117) e a uma disfunção da diferenciação e proliferação celular hipotalâmica (118,119), o que poderia explicar o aumento celular nos núcleos paraventricular, arqueado e ventromedial, que estão envolvidos no controle homeostático da ingestão alimentar. A alteração nos níveis de insulina e leptina ocorrida pela deficiência nutricional durante a gestação também parece contribuir para a disfunção hipotalâmica (118–120). Além disso, o *catch-up growth* pode exacerbar a disfunção metabólica ao longo da vida (121–123), modificando a expressão de receptores de sinalizadores envolvidos no controle do apetite, como a insulina, a leptina, a serotonina e a dopamina no hipotálamo (124). Alguns estudos mostraram que ratos com deficiência nutricional *in utero* têm alterações na expressão de genes e proteínas relacionados à sinalização dopaminérgica na área tegmental ventral, no núcleo accumbens e no córtex pré-frontal, regiões envolvidas no processamento do valor de recompensa (103,104,125). Existem também evidências de que a RCIU programe a sinalização opioide no sistema mesocorticolímbico, influenciando a resposta comportamental aguda frente ao

sabor doce (126,127). Portanto, esses resultados apontam que o desequilíbrio entre os sistemas de controle homeostático, hedônico e de recompensa podem estar associados com o consumo excessivo de alimentos hiperpalatáveis dos indivíduos que sofreram RCIU.

A alteração no comportamento alimentar na RCIU também pode ser explicada por uma disfunção no eixo hipotálamo-pituitária-adrenal, já que esses indivíduos possuem maior nível de corticosterona em diferentes idades (128–130), além de menor expressão de receptores de glicocorticoides e mineralocorticoides no hipocampo (131). Essas alterações podem levar a uma hiperatividade crônica desse eixo neuroendócrino, contribuindo para a programação de doenças metabólicas crônicas, assim como para uma resposta alterada ao estresse, o que pode influenciar o comportamento alimentar (132,133).

Além dessas evidências, o distinto comportamento alimentar dos indivíduos com baixo peso ao nascer possivelmente também venha em decorrência da disfunção de áreas envolvidas com processos cognitivos relacionados à alimentação. Por exemplo, há evidências de alteração da ativação (134) e da sinalização molecular (135) de áreas corticais em humanos e roedores, sendo que essa modificação está associada a uma atitude mais impulsiva frente aos alimentos. Sabe-se também que o hipocampo é uma das estruturas encefálicas que mais sofrem prejuízo com a exposição à desnutrição no período neonatal (136,137) e estaria envolvido com os desvios cognitivos apresentados pelos sujeitos que sofreram adversidade no ambiente pré-natal (52,138–140). Estudos recentes mostram que o hipocampo é fundamental para o controle inibitório frente a estímulos alimentares (141–143) e que essa estrutura cerebral tem papel fundamental na aquisição e evocação de memórias relacionadas à alimentação, na percepção de saciedade, na estimativa do tamanho e duração das refeições e no controle da ingestão induzida pelo estresse (144). Ainda, a resistência à insulina pode estar intimamente relacionada à disfunção hipocampal e ao desequilíbrio do comportamento alimentar na RCIU. Isso aumentaria o risco para o desenvolvimento de distúrbios metabólicos e adiposidade, conhecido como *vicious cycle of obesity* ou ciclo vicioso da obesidade. Este assunto será mais bem detalhado no artigo de revisão no item 4.2., que foi publicado na revista *Neuroscience & Biobehavioral Reviews* (145).

1.2. PROCESSOS COGNITIVOS RELACIONADOS À ALIMENTAÇÃO

A cada momento em que se ingere um alimento, existe a oportunidade de associá-lo às *food cues* ou pistas alimentares, que são os sinais preditivos da alimentação, como o odor, o sabor e o visual da comida, assim como o local, o horário, as emoções e os pensamentos antecipatórios à refeição (146). As respostas fisiológicas (como aumento da salivação, da insulinemia e da glicemia) ou psicológicas (como o desejo e o prazer de comer) que ocorrem durante a ingestão alimentar podem também acontecer na presença de qualquer estímulo preditivo do consumo. Esse fenômeno caracteriza a fase cefálica do comportamento alimentar e é conhecido como *food cue reactivity* ou responsividade à pista alimentar ou, então, como *external eating* ou alimentação induzida por estímulos externos (147,148). O aprendizado da associação entre os sinais preditivos e o consumo alimentar é uma forma de condicionamento clássico: as pistas alimentares (estímulo condicionado) tornam-se sinais para o consumo de alimentos (estímulo incondicionado) e a mera presença do estímulo preditivo do alimento passa a ser suficiente para induzir o aparecimento das expectativas e o desejo de ingeri-lo (149).

Muitos fatores influenciam a forma como os indivíduos respondem às pistas alimentares (143). Por exemplo, os alimentos são mais atrativos e saborosos quando se está com fome, sugerindo que os sistemas neurais hedônicos e de recompensa (áreas mesocorticolímbicas) interagem com os circuitos das vias homeostáticas do metabolismo (áreas tronco encefálicas e hipotalâmicas), influenciando no desejo e no prazer pela comida (150). Quando saciadas, pessoas obesas respondem mais fortemente às pistas alimentares do que as pessoas magras, indicando que o excesso de peso está associado a mudanças nos mecanismos cerebrais de recompensa dos alimentos (151–153). Além disso, variações genéticas da sinalização opioide e dopaminérgica parecem promover uma responsividade diferencial às pistas alimentares (154).

Vários estudos de neuroimagem sugerem que a capacidade de resistir a uma recompensa imediata em prol de um objetivo de longo prazo (como manter o peso corporal ou emagrecer) depende da ativação equilibrada de dois sistemas neurais: um sistema de decisão executiva envolvido no controle de impulsos, que corresponde à ativação das regiões lateral e medial do córtex pré-frontal, e um sistema para predizer o valor desta

recompensa, que corresponde à ativação do córtex orbitofrontal, do córtex pré-frontal ventromedial, do estriado e o do hipocampo (155–158). Além disso, tem-se sugerido que o equilíbrio entre os sistemas de controle inibitório e o de recompensa é afetado quando há outras demandas cognitivas concorrentes (159), ou quando há tentativas repetidas de autocontrole (160), talvez explicando porque os comedores restritivos muitas vezes exibem eventual ingestão excessiva e ganho de peso (161). Esse desequilíbrio entre os sistemas inibitório e o de recompensa também esclarece por que algumas pessoas são mais propensas a comer mais e ganhar mais peso do que outras (162–164). No entanto, ainda não está claro se as dificuldades com a inibição da responsividade às pistas alimentares preveem aumentos no peso corporal ou se esse o controle reduzido é uma consequência da obesidade.

Os processos de memória são fundamentais para o aprendizado dos desfechos prazerosos e saciadores da alimentação, pois as associações entre as pistas alimentares, o comportamento alimentar e as repercussões do consumo ao longo de experiências repetidas são armazenadas e sustentam a responsividade às pistas alimentares (143). Há evidências de que a memória de trabalho é importante para determinar a atenção que se presta às pistas alimentares, o que significa que pensar em um alimento aumenta a chances de perceber os estímulos no ambiente e a responder às pistas alimentares em comparação ao não pensar no alimento (165). Além disso, os estudos também sugerem que a memória episódica afeta as escolhas alimentares e as decisões sobre o quê, quanto e quando comer, pois, quando um alimento é identificado por uma pista no ambiente, a expectativa de sua ingestão é baseada em experiências passadas armazenadas, e outras informações, como o lugar, o momento e o contexto específico da alimentação também são evocadas (166,167). Usar estas memórias episódicas simula mentalmente o desfecho da escolha a ser tomada, permitindo selecionar o melhor resultado para determinado momento. Um importante ponto a ser considerado é que, com o passar do tempo, o comportamento frente às pistas alimentares torna-se mais habitual e as simulações baseadas nas memória ocorrem automática e inconscientemente quando em frente a uma escolha alimentar (168).

Ao reunir as evidências, o que se sugere é que as informações sobre refeições anteriores são combinadas com as informações sobre o estado interno pós-prandial atual, a

fim de ser feita uma previsão da saciedade e da recompensa futura, o que, então, modula a responsividade às pistas alimentares. Baseada nisso, a tendência para o consumo exagerado ou maior preferência por alimentos hiperpalatáveis pode resultar de um desequilíbrio entre o controle cognitivo alimentar (que depende da memória alimentar) e a responsividade habitual às pistas alimentares (169), provavelmente devido ao prejuízo nos processos de memória alimentar. Em um ambiente repleto de pistas de alimentos hiperpalatáveis, a ruptura do controle cognitivo pode levar ao ganho de peso ao longo do tempo e os estudos mostram que, de fato, o excesso de peso e a obesidade estão associados a problemas de aprendizagem e memória (170–175). Mais detalhes sobre a associação entre a memória alimentar e a obesidade são apresentados no artigo de revisão no item 4.2 desta tese (145).

1.3. MODELOS ANIMAIS DE RESTRIÇÃO DE CRESCIMENTO FETAL

A pesquisa científica com animais ocorre apenas quando é relevante para o avanço do conhecimento científico, considerando-se a impossibilidade de utilização de métodos alternativos, e essas técnicas devem ser refinadas a fim de reduzir o número e o desconforto dos animais utilizados para pesquisa (176,177). Para induzir a RCIU, os modelos animais são divididos em três categorias de intervenção: materna (por exemplo, pela limitação do consumo alimentar total ou proteico e pela diminuição da irrigação sanguínea no útero), placentária (por insultos de hipóxia) e fetal (através de manipulação genética ou infecções). As espécies mais utilizadas são ratos e camundongos, mas também existem pesquisas em cobaias, coelhos, cães, ovelhas, cabras, porcos, cavalos, babuínos e macacos Rhesus (178).

Há uma série de fatores espécie-específicos a serem considerados ao usar animais que mimetizem a gravidez humana, sendo que o número de filhotes por gestação, a forma de placentação, a duração da gestação, o parto e o desenvolvimento fetal *versus* neonatal afetam a escolha do modelo. Os roedores apresentam uma fisiologia semelhante aos humanos e a sua utilização em experimentos é vantajosa devido ao curto tempo de maturidade sexual (em torno de 60 dias), de ciclo estral (4 a 5 dias), de gestação (em torno de 21 dias) e do grande tamanho das ninhadas (em média, 8 filhotes por gestação), facilitando a observação entre gerações (179).

1.4. JUSTIFICATIVA

A literatura sugere que a programação do metabolismo e do comportamento alimentar e a posterior exposição a alimentos hiperpalatáveis possivelmente expliquem o risco aumentado para doenças crônicas relacionadas à obesidade dos indivíduos com baixo peso ao nascer. Especificamente, as evidências indicam que essa população é mais propensa à resistência à insulina e ao dano hipocampal e que a união desses fatores pode explicar, em parte, a disfunção no controle alimentar e na saúde metabólica.

Considerando a prevalência significativa de RCIU na população, a busca pelos mecanismos neurobiológicos envolvidos na programação do comportamento alimentar pelo ambiente intrauterino e pelo período pós-natal podem auxiliar na busca por intervenções precoces que estabeleçam o equilíbrio alimentar e a saúde ao longo da vida dos indivíduos nascidos pequenos para a idade gestacional.

2. OBJETIVOS

2.1. OBJETIVO GERAL

O objetivo geral deste trabalho foi testar a hipótese do ciclo vicioso da obesidade em indivíduos nascidos com baixo peso, investigando, através de um delineamento translacional, se a resistência à insulina estaria associada ao processamento cognitivo diferencial frente aos alimentos nestes sujeitos.

2.2. OBJETIVOS ESPECÍFICOS

a) Verificar o ciclo vicioso da obesidade, analisando se a resistência à insulina periférica estaria associada ao comprometimento da memória alimentar implícita e à desativação de áreas cerebrais associadas ao controle inibitório em resposta a imagens de alimentos hiperpalatáveis (parte I do artigo clínico em adolescentes representantes de todo o espectro de peso ao nascer);
b) Investigar se o baixo peso ao nascer estaria associado a um comportamento alimentar obesogênico e à alteração do tamanho hipocampal e da sensibilidade à insulina (parte II do artigo clínico em adolescentes nascidos com peso adequado ou pequeno para a idade gestacional);
c) Avaliar se o baixo peso ao nascer modificaria o estado metabólico, o comportamento alimentar e a função insulínica hipocampal, e se o consumo de alimentos hiperpalatáveis incrementaria essas mudanças (estudo experimental em um modelo de desnutrição gestacional em roedores).

3. CONSIDERAÇÕES ÉTICAS

A pesquisa experimental seguiu as Diretrizes e Normas Nacionais e Internacionais, especialmente a Lei nº 11.794, de 08 de outubro de 2008, que estabelece os procedimentos para uso cientifico de animais, e foi aprovada pela Comissão de Ética de Animais do Grupo de Pesquisa e Pós-Graduação do HCPA (número do projeto de pesquisa no GPPG: 13-0544) (Anexo 7.1).

A pesquisa clínica foi realizada de acordo com a Resolução 196/96 do Conselho Nacional de Saúde, além dos próprios regulamentos do Serviço de Gestão em Pesquisa do HCPA, aprovada pelo Comitê de Ética em Pesquisa do Grupo de Pesquisa e Pós-Graduação do HCPA (número do projeto de pesquisa no GPPG: 12-0254) e cadastrada na Plataforma Brasil (número do Certificado de Apresentação para Apreciação Ética: 5278112500005327) (Anexos 7.2 e 7.3).

4. ARTIGOS

4.1. CORRESPONDÊNCIA

Correspondence

obesity in women in developing countries might impact negatively on existing maternal health services in low-resource settings. Women with obesity have greater risk of pre-eclampsia, gestational diabetes, premature delivery, macrosomia, dystocia, post-partum haemorrhage, and miscarriage,[2] and their babies are at a 62% increased risk of dying within 48 hours after birth compared with newborn babies of mothers without obesity.[3] Caesarean section rates are higher in women with obesity, with three times more emergency caesarean sections, often associated with intra-operative and postoperative complications.[2,4]

For more on the 1000 Days Initative see http://www.thousanddays.org/

Additional equipment required includes larger cuffs for measuring blood pressure or theatre tables stable enough to tolerate additional weight. Skilled personnel are required for registering fetal heart beats, finding veins, or positioning in some women with obesity. Caesarean sections can be more difficult and additional help is often required to retract abdominal tissues. For spinal and epidural anaesthesia, failures and repeated pricking have been reported,[5] but longer spinal needles for such cases are often not available in low-resource settings. Post-partum and breastfeeding problems because of mechanical and endocrinological issues[6] in women with obesity require attentive nursing support. Based on these observations, targeted actions are required, as the problem of obesity in developing countries will rapidly increase in the coming years and services have to be prepared to avoid obesity related maternal morbidity and mortality.

For the *Lancet* Obesity Series see http://www.thelancet.com/series/obesity-2015

We declare no competing interests.

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The recent Obesity Series published in *The Lancet* considered the bigger picture of environmental factors. The authors of the Series emphasised and proposed important obesity prevention measures, including changing the environment, stimulating the expression of healthy food preferences, and establishing smart food policies.[1,2] Some individual factors play an essential part in the development of obesity and therefore should also be a target for obesity prevention. For example, it is well established that alterations in fetal growth increase the risk for developing obesity and its metabolic consequences later in life.[3,4] We and other groups have showed that fetal growth restriction modifies food preferences and feeding behaviour,[3] increasing spontaneous intake of highly palatable foods in individuals over the life-course. As acknowledged by Corinna Hawkes and colleagues,[1] although food preferences can be modified over time, they are often resistant to change. To us, the small picture—a healthy fetal life, optimised through adequate prenatal care—is essential to avoid the long-term consequences of fetal programming on childhood and adult health, including obesity.

It is important to avoid the idea that fetal growth restriction is simply the result of an inappropriate caloric intake during pregnancy. Many maternal factors affect fetal growth, such as hypertension, diabetes, smoking, and obesity.[4] Most of these conditions are treatable with good and frequent prenatal care. Despite being acknowledged in large campaigns such as the 1000 Days Initiative real prenatal care improvements are still very timid. In Brazil, for example, less than 62% of livebirths were preceded by at least 7 prenatal visits.[5] Besides health promotion and surveillance, prenatal care should be a time for parental orientation and teaching about breastfeeding, ideal weaning time and healthy weaning foods, which in the long term will also affect obesity risk. To provide such support, professional training is necessary, but not always available—this is another point where intervention or policy could have an enormous effect.

We declare no competing interests.

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The Lancet Series on obesity missed an important opportunity to more fully address non-Western food and the implications for policy and consumer engagement. While citing a few low-income and middle-income country examples, and noting the need for sociocultural dimensions

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Title: Tackling obesity: Challenges ahead

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In the recent Obesity Series published in The Lancet, the authors, considering the bigger picture of environmental factors, emphasized and proposed important obesity prevention measures, including changing the environment, stimulating the expression of healthy food preferences, establishing smart food policies, among others[1]. We highlight, however, that some individual factors play an essencial role in the risk for obesity and therefore should also be a target for obesity prevention. For instance, it is well established that alterations in fetal growth increase the risk for developing obesity and its metabolic consequences later in life. We and other groups have showed that fetal growth restriction modifies food preferences[2], as well as feeding behavior[3], increasing the spontaneous intake of highly palatable foods in individuals over the life-course. As well acknowledged by Hawkes et al[1], although food preferences can be modified over time, they are often persistent and

resistant to change. To us, the “small picture” – a healthy fetal life, optimized through adequate prenatal care – is essential to avoid the long-term consequences of fetal programming on childhood/adult health, including obesity.

It is important to avoid the misleading idea that fetal growth restriction is simply the result of an inappropriate caloric intake during pregnancy. Many prevalent maternal conditions as hypertension, diabetes and smoking affect fetal growth[4]. Even obese mothers can have fetal growth restricted newborns. Most of these conditions are amenable with good and frequent prenatal care. Despite being acknowledged in large campaigns such as the 1000 Days Initiative, real prenatal care improvements are still very timid. In Brazil, for instance, less than 62% of live births were preceded by at least 7 prenatal visits[5]. Besides health promotion and surveillance, prenatal care should be a time for parental orientation and teaching about breastfeeding, ideal weaning time and healthy weaning foods, which in the long term will also affect obesity risk. To provide such support, high professional training about these issues is necessary, but not always available – and this is another point where intervention/policy could have an enormous impact down the road.

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Review article

Hippocampal insulin resistance and altered food decision-making as players on obesity risk

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ABSTRACT

There are increasing evidences that hippocampus can modulate the decision of what, when and how much to eat, in addition to its already recognized role in learning and memory processes. Insulin also has been linked to brain functions such as feeding behavior and the imbalance of its mechanism of action on hippocampus is being related to cognitive dysfunction. The discussion here is whether changes in insulin action could contribute to intake dysregulation and obesogenic behavior as a primary consequence of impairing hippocampal functioning, aside from the role of this hormone on obesity development through peripheral metabolic pathways. Excess intake of high-fat and high-sugar diets leads to insulin resistance, which disrupts hippocampal function. Hippocampal physiology is sensitive to signals of hunger and satiety, inhibiting the ability of food cues to evoke appetite and eating, therefore alterations in hippocampal integrity could affect food inhibitory control leading to increased intake and obesity.

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1. Obesity: a growing concern

Obesity is considered pandemic as it occurs in a wide geographical area affecting an exceptionally high proportion of the population (Wylie-Rosett, 2004). The higher frequency of obesity was first observed in the United States but has spread to other industrialized countries and also occurs in developing countries

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Title: Hippocampal insulin resistance and altered food decision-making as players on obesity risk

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Abstract

There are increasing evidences that hippocampus can modulate the decision of what, when and how much to eat, in addition to its already recognized role in learning and memory processes. Insulin also has been linked to brain functions such as feeding behavior and the

imbalance of its mechanism of action on hippocampus is being related to cognitive dysfunction. The discussion here is whether changes in insulin action could contribute to intake dysregulation and obesogenic behavior as a primary consequence of impairing hippocampal functioning, aside from the role of this hormone on obesity development through peripheral metabolic pathways. Excess intake of high-fat and high-sugar diets leads to insulin resistance, which disrupts hippocampal function. Hippocampal physiology is sensitive to signals of hunger and satiety, inhibiting the ability of food cues to evoke appetite and eating, therefore alterations in hippocampal integrity could affect food inhibitory control leading to increased intake and obesity.

Key- words: Feeding behavior; cognitive decline; metabolic syndrome.

Obesity: a growing concern

Obesity is considered pandemic as it occurs in a wide geographical area affecting an exceptionally high proportion of the population (Wylie-Rosett, 2004). The higher frequency of obesity was first observed in the United States but has spread to other industrialized countries and also occurs in developing countries such as Brazil (Caballero, 2007). In 2014, 39% of the adults worldwide were overweight, and 13% were obese; rates that were twice as big as observed since 1980 (WHO, 2016)..

Obesity is characterized by body mass index of >30 kg per m2, which is mainly the result of an increase in fat mass. This condition occurs when there is an unbalance between calories that are consumed as compared to what is wasted and it can negatively affect health and decrease longevity (Flegal et al., 2013; Mitchell et al., 2011). The reasons why excessive intake occurs and how it leads to obesity are not fully understood, but it is known to involve genetic, physiological, metabolic, behavioral and cultural factors.

The concern about obesity relies on the fact that it is considered the fifth largest risk factor for disease worldwide, being a major risk factor for non-communicable diseases (Dulloo et al., 2010; Keller and Lemberg, 2003; WHO, 2016). Excess fat, especially in the central region of the body, is related to the most prevalent and costly current medical

problems such as type 2 diabetes, coronary artery disease, gastrointestinal problems, respiratory complications, osteoarthritis and various types of cancer (Haslam and James, 2005; WHO, 2016). Furthermore, obesity is closely associated with metabolic syndrome, which is characterized by hyperinsulinemia, insulin resistance, glucose intolerance, atherogenic dyslipidemia, hypertension, and increased expression of pro-thrombotic and pro-inflammatory markers (Olufadi and Byrne, 2008).

Obesity is also related to brain vulnerability and cognitive disorders, both in humans (Bruce-Keller et al., 2009; Galioto et al., 2013; Whitmer et al., 2005; Wolf et al., 2007) and in rodents (Bruce-Keller et al., 2009; Greenwood and Winocur, 2001; Winocur and Greenwood, 2005). As showed in many studies, obese humans (Benito-Leon et al., 2013) and rodents (Goldbart et al., 2006; Jurdak et al., 2008; Molteni et al., 2002; Park et al., 2010; Winocur and Greenwood, 1999) that consume hyperlipidemic and hypercaloric diets had inferior performance on learning and memory tests as compared to those with normal weight and to those who eat more healthy diets. In addition, clinical studies in humans show that abdominal fat and high body mass index are associated with reduced brain volume (Debette et al., 2010) and specific cortical thinning (Medic et al., 2016).

According to Sethi and Vidal-Puig (2007), there is an increased uptake of nutrients from the circulation to the periphery, particularly in insulin sensitive tissues shortly after food intake. During periods of fasting, the movement of molecules takes place in the opposite direction. In obesity, however, this bidirectional energy flow is altered due to endocrine dysfunction of adipose tissue and therefore decreases the effectiveness of endocrine mechanisms in the tissues (Caimari et al., 2010; Kahn et al., 2006; Lopez et al., 2003). Adipose tissue has humoral and hormonal regulation, and numerous functions, for example, insulation, physical barrier to trauma, energy storage and protein secretion with autocrine, paracrine and endocrine action. Secreted proteins, also called adipokines, can impact on biological aspects, including energy homeostasis, immune, cardiovascular, reproductive and neurological functions (Bruce-Keller et al., 2009; Sethi and Vidal-Puig, 2007). The extra supply of glucose and free fatty acids through exaggerated food intake with consequent increase in adipokines secretion (such as leptin and others) by adipose tissue growth, contributes to the onset of insulin resistance. This condition is characterized by

reduced biological action of insulin on target cells, with dysfunctions on uptake, metabolism and glucose storage at physiological concentrations of insulin (Kahn and Flier, 2000; Zeyda and Stulnig, 2009).

Many researchers are nowadays focusing in the association between insulin and the neurophysiology of hippocampus, an important region for learning and memory development and also eating behavior (Biessels and Reagan, 2015). Aside from the peripheral role of insulin on obesity development, we aim to discuss here a different way by which this hormone may, by acting centrally, influence obesogenic behavior and lead to excessive calorie intake. It is important to understand how metabolic and neural signals interact with each other on eating behavior. Thus, in this review we will focus on insulin action in the hippocampus and its consequent impaired memory related to food intake as well as the association between eating inhibition and insulin resistance.

Regulation of eating behavior

Animals must get enough food from its environment for its energy expenditure as an essential requirement for survival. The physiological state that makes an animal or a man seek food is called hunger. However, feeding behavior is not only an event that occurs to satiate hunger and that ends when hunger is finished throughout a metabolic feedback. A better way to describe feeding behavior is that it is controlled by homeostatic (bottom-up) but also hedonic (top-down) mechanisms, involving emotional, reward and cognitive factors.

Although the arcuate nucleus of the hypothalamus is one of the main areas of the central nervous system (CNS) responsible for the control of intake and energy homeostasis, feeding behavior is also modulated by the predicted reward values processed predominantly by the cortico-limbic structures (Berthoud, 2011). Deregulation of these systems leads to changes in consumption and predicts weight gain and obesity (Davis et al., 2011; Levitan et al., 2004; Silveira et al., 2016).

Memory of eating and obesity

In addition to the vast evidence that impulsive eating can result from an over-activation or a faulty signaling in the reward system components (Hebebrand et al., 2014; Johnson and Kenny, 2010; Luo et al., 2013; Volkow et al., 2011), some studies show that uncontrolled eating behavior can also be a result of a failure in cognitive inhibitory control related to food (Batterink et al., 2010; Bruce et al., 2010; He et al., 2014; Rangel, 2013). Food and its stimuli are cues that may evoke vigorous appetitive and consummatory responding on some occasions and little or no responding at other times. Thus, animals engage in appetitive and eating behavior until they become satiated and then refrain from making these responses until satiety wanes (Davidson et al., 2007; Davidson and Martin, 2014). Therefore, under conditions of negative energy balance, appetitive behaviors and food intake produce the rewarding effects of returning to homeostasis; however, once homeostasis is achieved, these behaviors no longer produce rewarding postingestive outcomes and could instead be followed by unpleasant consequences. According to some authors (Davidson et al., 2005), animals learn to anticipate both of these outcomes, and based on these associations, the food cues should excite or activate the stored representation of that reward (i.e., its memory) on subsequent occasions.

It has been shown that increasing awareness of food as it is eaten (Higgs and Woodward, 2009; Wansink and Payne, 2007), as well as simple recall of foods eaten at the last eating occasion decrease food intake in the following meal (Higgs, 2002). Robinson and colleagues (Robinson et al., 2013) suggest that these processes enhance episodic memory representation of the food consumed, and this information is used to process subsequent decisions about how much to eat (Brunstrom et al., 2012; Higgs, 2002; Higgs et al., 2012). Distraction exerts a greater influence on later intake than it does on immediate consumption, suggesting a larger effect as the memory of that eating episode fades (Robinson et al., 2013). In addition, it was shown that overweight adolescents have a memory bias in the recollection of high caloric food cues (that was not associated with better memory in general), suggesting a more elaborative encoding of this type of information or a bias at the retrieval stage of memory processing (Soetens and Braet, 2007).

Satiety regulation is a dynamic interaction process of peripheral signals such as hormones and different brain structures and neurotransmitter systems also involving the hippocampus. The hippocampus, classically associated with memory, is also recognized as a feeding behavior modulator (Parent et al., 2014) once it has many receptors for pre and post-prandial signals, such as insulin, leptin, ghrelin, glucose, cholecystokinin, glucocorticoids, NPY, galanin and bombesin (Lathe, 2001). In addition, the hippocampus receives neural signals related to food stimuli from different brain regions, such as the arcuate nucleus, nucleus of the solitary tract, insula and orbitofrontal cortex

(Wang et al., 2006) and sends efferent projections to other regions that can influence ingestive behavior, such as the hypothalamus, stria terminalis, and nucleus accumbens (Hsu et al., 2015; Kahn and Shohamy, 2013).

Hippocampal connectivity with striatum and neocortex throughout projections of parahippocampal region can also contribute directly to value assignment and decision-making in general, even without conscious awareness, dynamically modulating value representations during learning itself, allowing value to spread and biasing decisions without effortful retrieval at the time of decision (Wimmer and Shohamy, 2012). These properties could well influence food intake as the hippocampus has been suggested to be a discriminatory retention region for food cues. It is involved in the learned anticipatory response to environmental cues associated with eating (Davidson et al., 2007) and the inhibitory control of food intake and appetitive behavior depends on its structural integrity (Hebben et al., 1985; Rozin et al., 1998).

The influence of the hippocampus on food intake is mediated by adiposity signals, being related to the connection to the hypothalamus, and playing a role in body weight changes (Davidson et al., 2007), as shown in several rodent studies (Davidson et al., 2010; Forloni et al., 1986). Interestingly, overeating impairs hippocampal functioning, which contributes to the development and/or maintenance of diet-induced obesity in rodents (Davidson et al., 2013; Kanoski and Davidson, 2011). Hippocampal dysfunction increases meal frequency, total energy intake, and weight gain in rats (Davidson et al., 2010; Davidson et al., 2005). In humans, the famous H.M. case illustrates the importance of the hippocampus to integrate the information of internal metabolic states and willingness to eat; H. M., a patient that became amnesic after a bilateral resection in the medial temporal lobe region for epilepsy, had altered perception of internal states and would eat a second full dinner 1 min after he had completed the first one (Hebben et al., 1985).

Given that a host of life events that can impair hippocampal function, including excess intake of sugars and fats as shown in animal studies (Davidson et al., 2013; Freeman et al., 2011; Goldbart et al., 2006; Kanoski and Davidson, 2011; Kanoski et al., 2010; McNay et al., 2010; Molteni et al., 2002; Morris et al., 2016; Park et al., 2010; Tozuka et al., 2009) it is possible that diet-induced obesity is caused, at least in part, by impaired hippocampal inhibition of meal onset (Parent et al., 2014). Eating high-fat and high-sugar diets may impair hippocampal inhibitory control of eating behavior, perhaps because it becomes insensitive to satiety states and does not properly store information related to previous meal. The so called “western” diet seems to reduce hippocampus’ ability to resist

the environmental food cues (Davidson et al., 2007; Davidson and Martin, 2014) and increases the chance of overeating, excess weight gain, and more severe forms of cognitive impairment.

Physiological role of insulin

Insulin, a molecule composed by two polypeptide chains of 21 and 30 amino acids (Reid et al., 1968), is produced by pancreatic islets beta cells and is secreted into circulation with anabolic functions. This hormone promotes the deposition of substrates in the form of nutrients in tissues and, on the other hand, inhibits catabolism. Insulin promotes the transport of mainly glucose (but also amino acids and free fatty acids) from the extracellular compartment to inside the cells with consequent decrease in their circulating levels (Dimitriadis et al., 2011). Moreover, it can regulate the rate of carbohydrates used by most cells. Immediately after a high carbohydrate meal, the glucose absorbed into the blood may induce a rapid secretion of insulin (Aronoff et al., 2004) that promotes glucose uptake, storage and utilization by almost all body tissues, especially skeletal muscle, adipose tissue and liver (Pansuria et al., 2012). Also, insulin is responsible for inhibiting liver, kidney and small intestine glucose production in order to maintain glucose homeostasis (Wilcox, 2005).

Once released into the blood, insulin binds to a specific plasma membrane glycoprotein receptors on its target cells. Insulin receptor (IR) activation induces autophosphorylation of the tyrosine residues of the docking protein known as insulin receptor substrate (IRS), and leads to activation of several signaling cascades including phosphoinositide 3 kinase (PI3K)/Akt (at the metabolic tissue) and the mitogen-activated protein kinase (MAPK) pathways (Dimitriadis et al., 2011), that may increase or decrease the expression and the activity of IR. IR stimulates rapid glucose uptake in muscle, adipocytes, pancreatic and hepatic cells via translocation of glucose transporter type 4 (GLUT4) vesicles (Saltiel and Kahn, 2001) and also controls glycogen/lipid/protein synthesis, specific gene expression and energy metabolism (Pansuria et al., 2012). The MAPK pathway transmits a signal surface to the nucleus, controlling different biological responses such as cell growth, proliferation, differentiation, and cell death (Zhang et al., 2011). Of the six IRS families

described, IRS-1 and IRS-2 are involved in most of the effects of insulin in these two signaling pathways.

Insulin in the central nervous system

For a long time, it was believed that the brain was not insulin-dependent, but insulin and its receptors are found in abundance in the olfactory bulb, hypothalamus, and hippocampus, among other regions, both in humans and in rodents (Havrankova et al., 1978; Hill et al., 1986; Schulingkamp et al., 2000). Insulin is actively transported across the blood-brain barrier and it may even be produced locally in the brain, although most brain insulin is thought to be originated from the systemic circulation (Bingham et al., 2002; Ghasemi et al., 2013). Elevations in circulating insulin can alter brain function, augmenting the counter regulatory response to hypoglycemia (Fruehwald-Schultes et al., 1999). Physiologically relevant increases in plasma insulin levels also stimulate the translocation of GLUT4 to the plasma membrane in many CNS areas (McEwen and Reagan, 2004), even if the carrier is not as abundant in the CNS as GLUT1 and GLUT3 (Blazquez et al., 2014).

Many studies have shown a relationship between IR signaling and ion channels and receptors expression at synapses in various regions of the CNS, suggesting that insulin and IR can regulate synaptic plasticity and cognitive functions (Biessels and Reagan, 2015; Gispen and Biessels, 2000). Their location on hippocampal glutamatergic synapses indicates a role of insulin in the transmission and synaptic plasticity and modulation of learning and memory (Irvine et al., 2011; Muller et al., 2011; Skeberdis et al., 2001). In addition, IRS-1 inhibition is described in Alzheimer's disease and related animal models (Bomfim et al., 2012; Moloney et al., 2010), and the reversion of this inhibition improves cognitive outcomes in mice (Bomfim et al., 2012). It is also recognized the trophic function of insulin referred to proliferation, differentiation, and neurite growth (Lee et al., 2011; Xu et al., 2004).

Astrocytes are also known to express both IR and insulin signaling pathway proteins (Stern et al., 2014). Neurons from CNS depend on astrocytes for energy metabolism, maintenance of the blood-brain barrier, vascular reactivity, regulation of extracellular glutamate levels, protection from reactive oxygen species, amyloid-beta peptides, and

spread of inflammatory cells (Koistinaho et al., 2004; Zonta et al., 2003). Diabetes-related disturbances in the brain are associated with changes in astrocytes activity and can be prevented with insulin treatment (Coleman et al., 2010).

Moreover, insulin receptor signaling controls vessel dilation and contraction and regulates monocyte differentiation into macrophages (Baron, 1994; Laakso and Kuusisto, 2014; Pansuria et al., 2012), explaining why people with type II diabetes mellitus (T2DM) are more susceptible to central lesions, white matter hyperintensities, and brain atrophy than people without T2DM (de Bresser et al., 2010). Patients with T2DM also have increased levels of amyloid polypeptide deposits in and around blood vessels, which may be involved with their risk to develop vascular and neurological pathologies (Oskarsson et al., 2015). Insulin has also been shown to be important in maintaining the integrity and permeability of the blood-brain barrier (Hawkins et al., 2007; Sartorius et al., 2015).

Insulin in the hypothalamus and mesocorticolimbic system

Insulin is the major postprandial hormone and acts by moderating satiety signals generated by a meal in the brain tissue (Schwartz et al., 2000; Woods et al., 1998). It influences the amount of food consumed in a meal and also contributes to body weight regulation and reproduction (Bruning et al., 2000; Rodin et al., 1985).

Insulin is involved in feeding control and energy balance by regulating orexigenic and anorexigenic neurons (Palou et al., 2009). The IR is expressed by neurons in the arcuate nucleus and found both in POMC and AgRP neurons. In general, NPY/AgRP neurons are directly inhibited by insulin (as by leptin), while POMC/CART neurons are stimulated by these hormones (Mayer and Belsham, 2009). During the cephalic phase of eating behavior, peripheral changes in the insulin to glucose ratio are detected by these hypothalamic neurons, stimulating appetite by increasing the expression of both NPY and AgRP and decreasing POMC and CART expression (Berthoud and Jeanrenaud, 1982; Palou et al., 2009). During the gastric phase, insulin secretion is stimulated by gastrointestinal hormones such as CCK, but the release of insulin is higher when food is absorbed in the intestine (intestinal phase) and glucose levels rise. This increase in insulin due to increased glycemia during

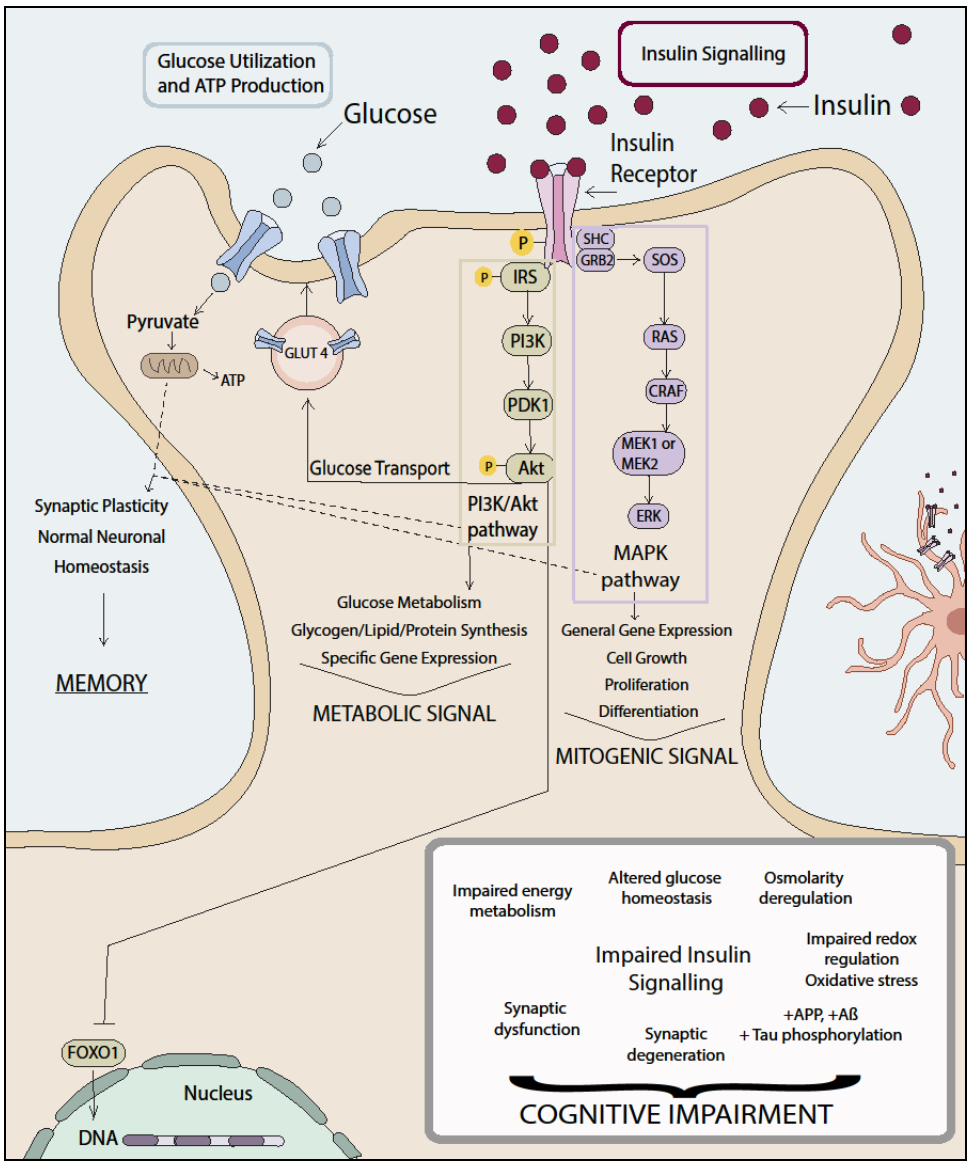

Figure 1. Insulin receptor activation on central nervous system (more specifically, in the hippocampus). Pancreas-derived insulin binds to receptors on endothelial cells of the blood-brain barrier, where it is transported into the brain interstitial fluid by a saturable process of receptor-mediated transcytosis. As soon as insulin binds its receptors (distributed throughout the cerebral cortex, hippocampus, hypothalamus, amygdala, olfactory bulb and septum) they become activated as a tyrosine kinase, leading to autophosphorylation of the IR subunits and phosphorylation of the tyrosine residues of its docking protein (insulin receptor substrate). This activates both the phosphoinositide 3 kinase (PI3K)/Akt and the mitogen-activated protein kinase (MAPK) pathways. The PI3K/Akt pathway seems to be associated with metabolic signaling, including an increase of glucose transporter from the GLUT4 translocation and subsequent conversion to ATP, while the MAPK pathway is associated with mitogenic signaling. Both these pathways of insulin signaling and glucose utilization are recognitablezed to be important for neuronal function and required for neuronal synaptic plasticity and for learning and memory. Impaired insulin signaling leads to synaptic dysfunction and altered glucose homeostasis that impacts energy metabolism, osmolarity, redox balance and could contribute to increased depots of amyloid precursor protein (APP), Aβ accumulation and tau hyperphosphorylation. These alterations lead to cognitive impairment and are accompanied by astrogliosis and possibly by neuroinflamation. Insulin receptor substrate (IRS); Phosphoinositide-dependent kinase-1 (PDK1); Protein kinase B (AKT); Phosphatidylinositol 3 kinase (PI3K); Growth factor receptor-bound protein 2 (GRB2); Son of Sevenless (SOS); Mitogen-activated protein kinase kinase (MEK); Extracellular signal-regulated kinase (ERK); Mitogen-activated protein kinase (MAPK); Forkhead box protein O1 (FOXO1). Adapted from (Verdile et al., 2015) and (Duarte, 2015).

postprandial state has an anorexigenic effect by acting on the same NPY and POMC hypothalamic neurons (Langhans et al., 2001; Palou et al., 2009). On the other hand, animals that lack or are insensitive to insulin are known to be hyperphagic and to gain weight, thus central administration of this hormone can reduce food intake and body weight (Gomez-Pinilla, 2008; Schwartz et al., 2000; Stockhorst et al., 2004).

Moreover, food intake is regulated via insulin in the mesolimbic system (Figlewicz, 2003; Figlewicz and Benoit, 2009), since there are IRs in the ventral tegmental area (VTA) and ventral striatum (Li et al., 2009; Mebel et al., 2012; Woods et al., 2016) as shown in experimental studies. Insulin suppresses dopamine release in the VTA, which decreases food "wanting" (Mebel et al., 2012). The decreased sensitivity to insulin in CNS limbic regions results in increased food consumption and in inaccurate valuation of foods, contributing to impulsive eating and obesity (Figlewicz et al., 2004; Woods et al., 2016). Another way by which insulin influences feeding behavior is modifying the sensory properties of food, by acting on olfactory mucosa and decreasing olfactory perception in rodents (Savigner et al., 2009) and humans (Ketterer et al., 2011).

Recent fMRI studies in humans suggest the existence of functional connections between the hypothalamus and different parts of the fronto-striatal circuitry of the brain (Kullmann et al., 2014). In addition, glucose ingestion increases the functional connectivity between the hypothalamus and the striatum, possibly via insulin (Page et al., 2013). Activity in the putamen, orbitofrontal cortex and insula correlate positively with enhanced peripheral insulin sensitivity via intranasal insulin application in humans (Heni et al., 2012; Kullmann et al., 2013a).

Finally, the prefrontal cortex plays an important role modulating feeding behavior and choices in humans, being involved in inhibitory control (lateral prefrontal cortex) (Hare et al., 2009) and reward-based decision-making (orbito-frontal cortex and anterior cingulate) (Rolls, 2004). All prefrontal regions are responsive to insulin (Guthoff et al., 2010; Heni et al., 2014a; Heni et al., 2012; Karczewska-Kupczewska et al., 2013; Kroemer et al., 2013; Page et al., 2013; Page et al., 2011). Exogenous intranasal insulin administration causes a decrease in the response of the prefrontal cortex to food pictures (Guthoff et al., 2010), and insulin increases after a glucose load are associated with reduced activation in frontal and limbic

regions (Kroemer et al., 2013). Therefore, brain insulin signaling in the striatal-frontal regions seems to act on value attribution and decision making negatively modulating food intake.

Insulin in the hippocampus

Insulin improves cognitive performance in humans and animals, including young healthy adults (Kern et al., 2001) and individuals with Alzheimer's disease (Chen et al., 2016; Freiherr et al., 2013), young rats (Haj-ali et al., 2009), aged rodents (Haas et al., 2016; Maimaiti et al., 2016) and animal experimental models with insulin resistance (Greenwood and Winocur, 2001; McNay et al., 2010). Studies using intranasal insulin administration show that this hormone is involved in cognition and particularly memory development (for a review, see (Ott et al., 2012)). Intracerebroventricular injection of insulin immediately after inhibitory avoidance training leads to memory enhancement 24h after training in rodents (Park et al., 2000). Intracerebroventricular or hippocampal injection of insulin also enhances spatial working memory and water maze memory dependent of PI-3K, increasing local glycolytic metabolism (Haj-ali et al., 2009; McNay et al., 2010; Stern et al., 2014). Furthermore, this hormone promotes neural growth in the hippocampus and the impairment of central insulin receptors is associated with learning and memory deficits (Stockhorst et al., 2004). Additionally, hippocampal-dependent spatial learning tasks, such as the Morris water maze, increase the hippocampal IR signaling in rodents (Zhao et al., 1999). These data highlight that IR cascade activation in the hippocampus is associated with cognitive performance (Cholerton et al., 2013).

The hippocampal development is particularly sensitive to changes in glucose homeostasis (Amin et al., 2013). As in the periphery, central insulin action results in translocation of the neuronal insulin-sensitive GLUT4 to the plasma membrane of hippocampal neurons (Grillo et al., 2009), which increases their glucose uptake. It also decreases glucose extracellular levels, and increases lactate levels in the extracellular space, indicating an increase in local glycolytic metabolism (McNay et al., 2010). Hippocampal cell culture experiments suggest that the dendritic distribution of insulin receptors is in accordance with a synaptic localization (De Felice et al., 2009; Zhao et al., 2008). Insulin also induces synaptogenesis, modulates the synaptic function, and regulates dendritic spine formation and excitatory synapse development in hippocampal neurons through the

activation of PI3K/mTOR pathway (Lee et al., 2011; Lee et al., 2005) and upregulation of tau protein (Nemoto et al., 2011).

N-Methyl-D-Aspartate receptors (NMDARs) are part of the ionotropic glutamate receptors family and glutamate is known as the major excitatory neurotransmitter of the nervous system (Paoletti et al., 2013). The specific patterns of neuronal activity occurring by calcium flow through these receptors are converted into long-term changes in synapse structure and function, essential for memory, behavioral inhibition and other cognitive functions (Baker and Kim, 2002; Taylor et al., 2014). In hippocampal synapses, the NMDARs complex in the post-synaptic density (PSD) is a structure intimately involved in the regulation of synaptic plasticity (Gardoni et al., 2002). The impairment of synaptic plasticity in streptozotocin (STZ)-induced diabetic rats is associated to an inappropriate level of NMDARs stimulation required for the induction phase of long-term potentiation. In fact, insulin can potentiate current flow through NMDA, and the Tyr-phosphorylation of the subunits GluN2A and GluN2B of the NMDARs, an important component of signal transduction mechanisms occurring in PSD, is mediated by insulin in hippocampal slices (Christie et al., 1999). Additionally, IR and the insulin receptor substrate-1, 2 and p58/p53 (IRS-1, 2, and p58/p53) are components of PSD (Abbott et al., 1999). In mice that lack IRS-2, there is a deficit in NMDA receptor-dependent synaptic plasticity in the hippocampus, with concomitant deficits in the modulation of synaptic plasticity, and these changes are associated with reduced basal phosphorylation of the NMDA receptor subunit GluN1 as well as downstream targets of the PI3K pathway (Costello et al., 2012). This suggests that insulin modulates synapse plasticity by stimulating long-term depression and potentiation, which are involved in memory representation (Feldman, 2009) reviewed in (Moult and Harvey, 2008).

The expression and concentration of GluN2B are significantly reduced in hippocampal PSD in STZ-treated rats (Di Luca et al., 1999; Muller et al., 2011) (Di Luca et al., 1999; Muller et al., 2011), but insulin can prevent the decreased Tyr-phosphorylation in hippocampal pyramidal cells of these animals (Gardoni et al., 2002). The disturbances of the NMDARs on STZ-diabetes are the result of a slowly progressive process, rather than an acute insult caused by hyperglycaemia, and at least part of the learning and plasticity deficits in STZ-rats may be a direct consequence of disturbances at the level of the NMDARs complex.

Interestingly, human fMRI studies show a significant positive correlation between fasting plasma insulin levels and hippocampal activity after stimulation with high-caloric food images strongly suggesting a link between insulin signaling pathways, hippocampal activation, and craving behavior to food cues in humans (Avena et al., 2008; Hargrave et al., 2016; Pelchat et al., 2004; Wallner-Liebmann et al., 2010). Hippocampal neighboring gyri (parahippocampal and fusiform gyri) are linked to neural pathways of visual recognition, especially visual food cues (Kullmann et al., 2013b; van der Laan et al., 2011), being particularly sensitive to insulin. These findings corroborate the idea that the hippocampus participates in the identification of external signs of food and that insulin is closely linked with that role of the hippocampus in feeding behavior, possibly reducing the attention to food cues (Kullmann et al., 2016).

Implications of insulin resistance

There are many factors that can explain the mechanisms of insulin resistance, including obesity, inflammation, mitochondrial dysfunction, hyperinsulinemia, lipotoxicity/ hyperlipidemia, genetic background, endoplasmic reticulum stress, aging, oxidative stress, fatty liver, hypoxia, lipodystrophy, and pregnancy (Ye, 2013). In obesity, the increase in glucose and free fatty acids by high food intake, as well as by adipose tissue growth products including hormones such as leptin and cytokines, contribute to the onset of insulin resistance (Kahn et al., 2006). In obese individuals, adipose tissue releases increased amounts of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines, and other factors that are involved in the development of insulin resistance (Hotamisligil, 2003).

This dysfunction occurs when insulin-sensitive tissues progressively become less responsive to insulin and, consequently, insulin-induced glucose uptake is impaired. The failure may be the result of changing insulin signaling in target tissues (reduced concentration and kinase activity of IR, limited concentration and phosphorylation of IRS-1 and 2 of PI activity 3-kinase, low GLUT4 translocation and diminished activity of intracellular enzymes). In addition there is a down-regulation of GLUT4 in adipocytes (Petersen and Shulman, 2006). Thus, there is a dysfunction in glucose uptake, metabolism and storage

under physiological concentrations of insulin and, therefore, increased production of this hormone by the pancreas (Kahn and Flier, 2000). In many progressive cases, the lipids deposits into pancreatic islet cells impair the ability of beta cells to maintain enhanced insulin secretion, leading to glucose intolerance and type 2 diabetes (Cerf, 2013; Haslam and James, 2005).

Central implications of insulin resistance

In humans, one of the first studies to show that, the brain was unresponsive to insulin in situations of obesity was published in 2006 (Tschritter et al., 2006). The benefits promoted by insulin centrally are not found in situations of resistance of this hormone (Biessels and Reagan, 2015; Kullmann et al., 2016; Lee et al., 2016; Stoeckel et al., 2016). In this condition, glucose metabolism and insulin signaling are impaired in many brain regions, including those involved in learning and memory, such as the hippocampus (Biessels and Reagan, 2015; Pearce et al., 2012). Patients with type II diabetes have reduced performance in almost all neuropsychological tests, especially in memory, information processing speed and executive function (Moheet et al., 2015). In obesity and Alzheimer's disease, and aging itself, there is a change in the ratio of central and peripheral levels of insulin, wherein the concentration of the hormone in the periphery is higher as compared to healthy and younger individuals (Rani et al., 2016; Stockhorst et al., 2004). It is also known that there is lower transport of peripheral insulin to the brain under these conditions, although some studies show that the reduction of insulin signaling is not generalized to all brain regions and for all existing signaling pathways at the same time (Steculorum et al., 2014).

In human neuroimaging studies, patients with obesity or type II diabetes exhibit reduction in gray matter volume and in cortical thickness, as well as loss of white matter integrity (Bischof and Park, 2015; Brundel et al., 2014), particularly in limbic structures such as the hippocampus and amygdala (den Heijer et al., 2003; Hajek et al., 2014; Manschot et al., 2006). They also have altered brain activation and functional connectivity in different brain networks, including areas involved with working memory (Qiu et al., 2016; Zhang et al., 2016). Reduction in the volume of the hippocampal formation is seen in individuals with impaired glucose tolerance and insulin resistance (Convit et al., 2003; Ursache et al., 2012),

and deficits in hippocampal-based memory performance and preservation of other cognitive domains are observed in these patients (Gold et al., 2007). Obese adolescents with type II diabetes have reduced cognitive performance in verbal memory and psychomotor efficiency, accompanied by reduced white matter volume and increased ventricles observed on MRI (Yau et al., 2010). In postmenopausal women, it was found a negative correlation between insulin resistance indexes such as HOMA-IR (Homeostasis Model of Assessment - Insulin Resistance) and hippocampal volume, as well as cognitive performance in tests of declarative and non-declarative memory (Rasgon et al., 2011). Patients with type II diabetes (Hoogenboom et al., 2014; Musen et al., 2012) and obese individuals (Kullmann et al., 2012) show diminished connectivity in the default mode network (DMN), a network including the precuneus, prefrontal cortex, lateral temporal cortex and hippocampus, that is essential for higher cognitive processes such as memory and cognitive function. Interestingly, the use of insulin in type II diabetes patients increases the functional connectivity between the hippocampus and frontal regions (Gottschalk and Ellger, 2015; Zhang et al., 2015), and this enhanced functional connectivity correlates with better performance in cognitive tests (Zhang et al., 2015).

Insulin resistance reduces peripheral insulin transport and its uptake into the brain (Plum et al., 2005; Stockhorst et al., 2004), turning the neurons less able to use glucose. In animal studies, this cell disorder is associated to impairment in normal neural transmission and electrophysiology, as well as to learning and memory due to hippocampus damage (Amin et al., 2013; Gardoni et al., 2002; Grillo et al., 2009). This is in accordance to other studies using the consumption of high-fat and/or high-sugar diets in animal models of obesity and insulin resistance (Davidson et al., 2012; Dinel et al., 2011; Jurdak et al., 2008; Kanoski et al., 2010; Kohjima et al., 2010; Molteni et al., 2002; Stranahan et al., 2008; Winocur and Greenwood, 2005). Insulin-induced long-term depression is attenuated in these animals (Mielke et al., 2005), especially in the hippocampus (Pratchayasakul et al., 2011), suggesting that brain insulin resistance contributes to cognitive impairment.

The combination of impaired insulin receptor signaling and decreased insulin transport across the blood-brain barrier (Davidson et al., 2012; Kanoski et al., 2010) can lead to hippocampal insulin resistance (Biessels and Reagan, 2015), which includes decreases in

insulin-stimulated phosphorylation of IR and Akt, less insulin-stimulated translocation of GLUT4, as well as increased serine phosphorylation of IRS-1, a marker of insulin resistance (Arnold et al., 2014; Mielke et al., 2005). Experimental studies in rodents show that this imbalance of insulin mechanism of action on the hippocampus can be explained by mitochondrial dysfunction, increased reactive oxygen species production, caspases inhibition, disturbances in the expression of apoptosis regulator genes, impairments in hypothalamic–pituitary–adrenal axis function, and neuroinflammation (Boitard et al., 2014; Dinel et al., 2011; Morrison et al., 2010; Pipatpiboon et al., 2013; Piroli et al., 2007; Sadeghi et al., 2016). However, these factors may also act independently of IR, causing hippocampal neuroplasticity deficits and neuronal apoptosis in obesity and elderly (Tucsek et al., 2014). Together, these phenomena increase neuronal damage and collaborate for the low cognitive performance in obese individuals.

Additionally, it was found that obesity and insulin resistance result in reduced hippocampal expression and signaling of the brain derived neurotrophic factor (BDNF) in several studies (Molteni et al., 2002; Park et al., 2010; Tozuka et al., 2009), which is known to play important roles in proliferation, differentiation and survival of neurons during development, as well as in the synaptic activity and plasticity in many groups of mature neurons, being also anorexigenic (Lebrun et al., 2006). On the other hand, treatment with hypoglycemic agents and insulin sensitizers, as peroxisome proliferator-activated receptor-γ (PPARγ) agonist, metformin, and inhibitors of dipeptidyl peptidase 4 (DPP-4), reduces brain mitochondrial dysfunction and reverses memory impairments in high-fat induced insulin resistant rats (Pintana et al., 2012; Pipatpiboon et al., 2013; Pipatpiboon et al., 2012).

Network hubs and modulators

As reviewed in the previous sections, a decreased connectivity within the default mode network, including the hippocampus, posterior cingulate cortex/precuneus and prefrontal regions in seen in patients with type II diabetes (Hoogenboom et al., 2014; Musen et al., 2012) and could explain the cognitive deficits associated with this condition. This core network has a functional connection to both lateral and medial hypothalamus (Kullmann et

al., 2014), and this may constitute the link between the peripheral metabolism and higher cognitive function and its effects on food choices and feeding behavior.

Another possible link between peripheral metabolism and eating behavior central control relies on the mesocorticolimbic pathways, as the VTA dopaminergic neurons have insulin receptors (Figlewicz, 2003; Li et al., 2009), and activity in the striatum correlates with enhanced peripheral insulin sensitivity (Heni et al., 2012). Insulin acting on these neurons could modulate feeding preferences as suggested in experimental studies (Portella et al., 2015).

Elevated proinflammatory cytokines, such as TNF alfa, interfere with insulin signaling and contribute to insulin resistance (Ferreira et al., 2014). Peripheral chronic low-grade inflammation is a feature of obesity and type II diabetes, being associated with hypothalamic gliosis (Thaler et al., 2012), loss of hypothalamic structural integrity (Cazettes et al., 2011; Puig et al., 2015), and inferior cognitive performance (Puig et al., 2015). Therefore, inflammation is an important modulator of insulin action and a possible link between metabolic disorders and cognitive decline.

Impaired brain insulin action could also result from insulin resistance at the blood-brain barrier (Verdile et al., 2015), or changes in the transport ratio of insulin across the blood-brain barrier (Heni et al., 2014b; Sartorius et al., 2015). These processes are seen during aging (Shah and Mooradian, 1997). In animal models, exposure to high-fat diets leads to increased blood-brain barrier permeability and cognitive dysfunction (Davidson et al., 2012; Pallebage-Gamarallage et al., 2012), suggesting that blood-brain barrier injury is another contributing factor to the development and progression of cognitive impairment in insulin resistant states.

Hippocampal insulin resistance and altered food decision-making – role on obesity risk

In this review, we propose to approximate two sets of evidence that appeared to have a very reasonable association. On the one hand, the contribution of the hippocampus on

food decision-making and, on the other, the role of insulin in the healthy functioning of the hippocampus. Both phenomena collaborate to balance food intake and body dimension. However, a disruption of the equilibrium that occurs in insulin resistant states may lead to a vicious cycle of obesity (Davidson et al., 2005; Davidson and Martin, 2014; Kanoski and Davidson, 2011): diets rich in fat and sugar induce an increase in adipose tissue; this leads progressively to insulin resistance, at least in some regions of the CNS; hippocampus is affected by the imbalance in insulin receptor signaling; the memory related to food is altered; there is no further inhibition to food stimuli, even when already satiated; hyperphagia leads to obesity in a feed forward process.

We reviewed evidence showing that hippocampal damage can disrupt interoceptive state signals ability to modulate eating behavior, leading to increased appetitive responding. Findings that satiety neuropeptides such as insulin play a role in the performance of hippocampal-dependent learning and memory processes encourage speculation that the effects of these neuropeptides on food intake might be based in part on their effects on behavioral inhibition processes that are mediated by the hippocampus (Benoit et al., 2010; Wimmer and Shohamy, 2012). Additionally, there are evidences that insulin resistance can be strongly involved with hippocampal damage.

Individuals vulnerable to uncontrolled eating show insulin resistance in the prefrontal cortex (Kullmann et al., 2015) and hippocampus (Convit et al., 2003) and altered measures of cognition related to eating behavior, such as disinhibition and food craving. The homeostatic control of food intake works in close interaction to regions involved in decision-making and value attribution (Berthoud, 2012). Therefore, in agreement with Biessels & Reagan (Biessels and Reagan, 2015), we can suggest that memory impairment for a consumed meal, which can harm the stability of feeding patterns (Epstein et al., 2010), is an early sign associated with hippocampal insulin resistance. This specific cognitive deficit may contribute to increased food intake, leading to overeating, obesity and higher insulin resistance in long term, as a “vicious cycle” model proposed by Martin and Davidson (Davidson and Martin, 2014; Martin and Davidson, 2014). The development of tools and protocols to detect subtle behavioral characteristics associated with increased risk for developing obesity and related metabolic disturbances (e.g. behavioral tasks and cognitive testing that could lead to a

better comprehension of the role of memory on food patterns) can be of interest for target prevention and counseling.

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4.3. ARTIGO CLÍNICO

Artigo na versão pré-submissão.

Title: The vicious cycle of obesity: insulin sensitivity and cognitive processes involved in eating behavior of individuals born small for gestational age

Or: Diminished insulin sensitivity is associated with altered brain activation to hyperpalatable food images and with risky feeding behavior for obesity in individuals born small for gestational age

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Abstract: Impairments in fetal growth are associated with a greater risk for developing obesity-related diseases in adulthood, preceded by a preference for eating hyperpalatable foods. As proposed in the “vicious cycle of obesity” framework, excessive intake of hyperpalatable foods leads to insulin resistance, disruption in cognition and hippocampal function, and further altered feeding behavior. We hypothesized that variations in insulin sensitivity would be correlated with differential brain activation facing hyperpalatable food cues in healthy adolescents, as well as associated with variations in implicit memory for food choices. Moreover, we sought to explore the presence of this vicious cycle in a sample of adolescents classified according with the presence or absence of impaired fetal growth. Fetal growth was based on birth weight ratio and those in the lower tertile of the distribution were considered small for gestational age. After blood sample collection, all participants could choose foods as a snack offered in the research center cafeteria. Implicit, non-declarative food memory was tested 6 months later through the evaluation of a series of photos of snacks. Feeding behavior was also assessed by the nutritional composition of the snack chosen, 24h Dietary Recall, Food Frequency and Dutch Eating Behavior questionnaires. Furthermore, brain responses to hyperpalatable foods were investigated using a functional magnetic resonance imaging task showing hyperpalatable versus healthy foods or versus non-food objects images. Brain structural MRI volumetry was also analyzed. HOMA-IR index correlated positively with activation in the cuneus, and negatively with activation in the left middle frontal lobe, superior frontal gyrus and precuneus when facing hyperpalatable foods versus non-food objects images. In addition, HOMA-IR index and insulinemia were higher in participants who did not choose their original snack compared to those who chose their own snack. Subjects who were born with impaired fetal growth had higher snack caloric density, greater chance of not choosing their own snack and bilateral reduction in the hippocampal subiculum. In addition, there is an interaction between HOMA-IR and birth weight ratio for

external eating behavior. We suggest that diminished insulin sensitivity correlated with activation in areas of visual attention and inactivation of areas associated with inhibitory control in healthy adolescents. Insulin sensitivity also associated with less consistency in implicit memory for a consumed meal, which may suggest lower ability to establish a dietary pattern, and can contribute to the development of obesity. Besides that, insulin sensitivity and hippocampal alterations are associated with differences in feeding behavior described for low birth weight individuals, suggesting that cognition and hormone regulation are important components involved in food intake modifications in this vulnerable population.

Key-words: Poor fetal growth; Intrauterine growth restriction; Gestational nutritional deprivation; Feeding behavior; External eating; Food memory; MRI; Subiculum; HOMA-IR index; Metabolic syndrome.

4.4. ARTIGO EXPERIMENTAL

Artigo na versão pré-submissão.

Title: Hippocampal insulin sensitivity and behavioral reactivity to food cues in adult rats exposed to poor fetal growth

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Abstract: Despite the known impact of poor fetal growth on metabolism and cognitive function, little is known about the molecular mechanisms that link the altered feeding behavior to metabolic syndrome. This study investigated whether exposure to poor fetal growth followed by chronic palatable food availability in rats affects (1) insulin-dependent hippocampal function and (2) food memory and feeding predictability, as well as if it is associated with the development of metabolic alterations. On 10th day of pregnancy, rats were divided into control group (Adlib), which continued with standard chow ad libitum, and experimental group (FR), which received 50% of the chow intake of Adlib. At birth, male pups were adopted by Adlib mothers and, at 60 days, half of offspring from each group received high-fat and sugar (HFS) diet and half continued with standard (CON) diet. At 140 days, behavioral tasks started, and, at 200 days of age, tissues were collected. When restricted animals were chronically fed with hyperpalatable diet, they were capable of recognizing food novelty, an ability that was associated with hyperinsulinemia and higher body weight gain during experiment. Poor intrauterine growth also reduced eating and feeding entropy when predictability of food reward was changed, suggesting functional alterations in the hippocampus. Rats with poor fetal growth had pre-insulin resistant state, with altered hippocampal signaling and increased glutamatergic receptor subunit phosphorylation induced by insulin systemic injection. These findings indicate that poor fetal growth together with chronic hyperpalatable food exposure induces changes in hippocampal insulin sensitivity, and this may be reflected in risky eating behaviors favoring body weight gain.

Key-words: Intrauterine growth restriction; Small for gestational age; Feeding behavior; Food memory; Metabolic syndrome; Palatable food; Animal model

5. CONSIDERAÇÕES FINAIS

Esta tese de Doutorado teve como objetivo geral testar a hipótese do ciclo vicioso da obesidade em indivíduos nascidos com baixo peso, investigando, através de um delineamento translacional, se a resistência à insulina estaria associada ao processamento cognitivo diferencial frente aos alimentos nestes sujeitos. Os pressupostos desta hipótese foram inicialmente discutidos e revisados na carta ao editor *Tackling obesity: challenges ahead* e no artigo de revisão *Hippocampal insulin resistance and altered food decision-making as players on obesity risk*.

No artigo clínico *The vicious cycle of obesity: insulin sensitivity and cognitive processes involved in eating behavior of individuals born small for gestational age*, o primeiro objetivo foi investigar se a sensibilidade à insulina estaria correlacionada à ativação cerebral diferencial frente a imagens de alimentos hiperpalatáveis, assim como se estaria associada a variações na memória implícita alimentar, em adolescentes saudáveis representando todo o espectro de peso ao nascer. Os resultados mostraram que o índice de resistência à insulina se correlacionou positivamente com a ativação do cúneo, região reconhecida na atenção visual, e negativamente com o lobo frontal médio esquerdo, giro frontal superior e precúneo, áreas com papel no controle cognitivo inibitório, quando imagens de alimentos hiperpalatáveis eram visualizadas, em comparação à visualização de objetos neutros. Além disso, o índice de resistência à insulina e a insulinemia apresentaram-se mais altos nos indivíduos que não escolheram o seu lanche consumido meses antes no teste de escolha do lanche, mostrando prejuízo na memória alimentar implícita. Com esses dados, sugeriu-se que a sensibilidade à insulina está correlacionada com o processamento cognitivo alimentar, podendo fazer parte da modulação do comportamento alimentar de risco para doenças relacionadas à obesidade.

O artigo clínico também teve como objetivo averiguar se o baixo peso ao nascer estaria associado a um comportamento alimentar obesogênico e à alteração do tamanho hipocampal e da sensibilidade à insulina em adolescentes. Foi encontrado que os indivíduos nascidos com baixo peso consumiram alimentos com maior densidade calórica e

apresentaram prejuízo na memória alimentar implícita e menor volume do subículo hipocampal. Ainda, a interação entre o índice de resistência à insulina e a razão de peso ao nascer prediz a ingestão alimentar externa. A partir dessas evidências, concluiu-se que alterações no hipocampo e na sensibilidade à insulina estão associadas às diferenças no comportamento alimentar de indivíduos pequenos para a idade gestacional, o que indica que os processos cognitivos e a regulação hormonal parecem ser elementos da ingestão alimentar de risco para complicações metabólicas destes sujeitos.

O artigo experimental *Hippocampal insulin sensitivity and behavioral reactivity to food cues in adult rats exposed to poor fetal growth* investigou se a restrição fetal induzida por desnutrição gestacional em ratos teria implicações na função hipocampal dependente de insulina, na memória e previsibilidade alimentares, no consumo de dieta hiperpalatável e no estado metabólico e peso corporal. Além disso, verificou se a exposição crônica à dieta hiperpalatável influenciaria nesses desfechos. Encontrou-se o baixo peso ao nascer associado ao um estado de pré-resistência à insulina hipocampal, ao aumento na fosforilação do receptor glutamatérgico dessa região induzida por insulina e a reduzidas ingestão e entropia quando a previsibilidade da recompensa alimentar hiperpalatável foi alterada. Quando os animais restritos ingeriram cronicamente a dieta hiperpalatável, foram capazes de reconhecer a novidade alimentar e apresentaram maior peso corporal ao longo do experimento. Esses resultados indicaram que o baixo peso ao nascer altera a função insulínica hipocampal e, quando, associado à ingestão crônica de dieta hiperpalatável, parece alterar o comportamento alimentar em favor do ganho de peso corporal.

Com base nas evidências encontradas e sintetizadas na Tabela 1, sugere-se que a resistência à insulina parece (a) modificar a habilidade de estabelecer um padrão alimentar e (b) estar associada às modificações funcionais do hipocampo no baixo peso ao nascer, (c) o que pode explicar as mudanças de comportamento alimentar nesta população. Portanto, as evidências sustentam a hipótese de que os indivíduos nascidos com baixo peso seriam mais propensos ao ciclo vicioso da obesidade, indicando que a resistência à insulina pode estar modulando as funções hipocampais que participam dos processos cognitivos frente aos alimentos (Figura 1): desde a infância, são mais sensíveis à insulina e preferem alimentos

hiperpalatáveis; a maior ingestão desses alimentos induz progressivamente a resistência à insulina; a alteração na sinalização de insulina hipocampal prejudica a formação da memória alimentar e o controle inibitório frente a pistas alimentares; o maior consumo crônico de alimentos hiperpalatáveis rompe o equilíbrio e surgem as doenças metabólicas relacionadas à obesidade na vida adulta.

Tabela 1. Principais evidências e conclusões da pesquisa empírica.

Artigo clínico – parte I	Artigo clínico – parte II	Artigo experimental
Evidências: - A maior resistência à insulina está associada ao comprometimento da memória alimentar implícita; - Quanto maior a resistência à insulina, maior ativação de áreas cerebrais associadas à atenção e menor ativação das associadas ao controle inibitório em frente a imagens de alimentos hiperpalatáveis. **Conclusões:** A resistência à insulina sugere modificar a habilidade de estabelecer um padrão alimentar.	**Evidências:** - O baixo peso ao nascer está associado ao comprometimento da memória alimentar implícita; - A resistência à insulina interage com o peso ao nascer ao modular a ingestão alimentar externa; - O baixo peso ao nascer está associado à redução do volume do subículo hipocampal; - O baixo peso ao nascer está associado a uma ingestão mais densamente calórica. **Conclusões:** A resistência à insulina e as modificações estruturais do hipocampo podem ter um papel no comportamento alimentar alterado dos indivíduos com baixo peso ao nascer.	**Evidências:** - O baixo peso ao nascer junto à ingestão crônica de dieta hiperpalatável está associado ao reconhecimento da novidade alimentar; - O baixo peso ao nascer está associado a menor ingestão e reduzida entropia quando há mudança na previsibilidade alimentar; - O baixo peso ao nascer está associado à resistência à insulina hipocampal e essa associação é incrementada quando junto à ingestão crônica de dieta hiperpalatável; - O baixo peso ao nascer está associado ao aumento da fosforilação do receptor glutamatérgico hipocampal induzido por insulina; - O baixo peso ao nascer junto à ingestão crônica de dieta hiperpalatável está associado ao maior ganho de peso corporal. **Conclusões:** A restrição de crescimento fetal está associada à alteração na função insulínica do hipocampo, sendo mais evidente com a ingestão de dieta hiperpalatável, o que pode explicar as mudanças de comportamento alimentar e maior ganho de peso corporal.

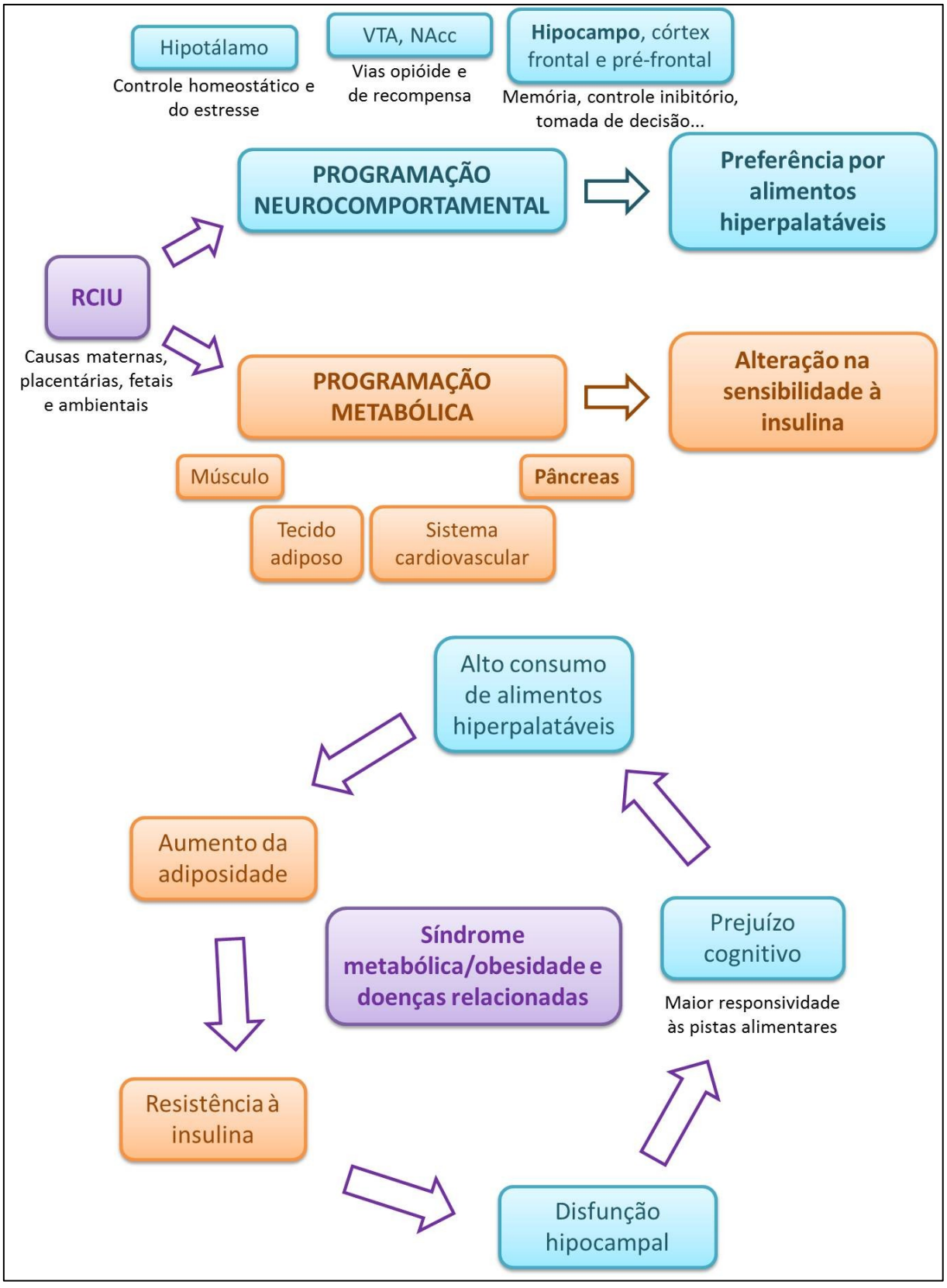

Figura 1. O ciclo vicioso da obesidade na restrição de crescimento intrauterino.

Convém considerar que o comportamento alimentar é influenciado não apenas por fatores genéticos e epigenéticos, mas também por questões culturais, e que as ciências biomédicas trabalham principalmente com probabilidades. Por tanto, os indivíduos nascidos com restrição de crescimento intrauterino não estão predeterminados às doenças metabólicas, mas possuem maior chance de desenvolvê-las do que a população em geral. As implicações dos achados desta tese estão, principalmente, em destacar a importância da vida alimentar precoce, já que é o período em que ocorre o aprendizado e o estabelecimento de hábitos alimentares saudáveis, através dos processos cognitivos relacionados à alimentação, dentre eles as memórias alimentares implícitas. A qualidade do padrão alimentar, que é influenciado pelo ambiente nutricional *intrautero* e modelado durante a vida pós-natal (78,79,180–183), pode prevenir ou aumentar a predisposição a disfunções e doenças crônicas não transmissíveis na idade adulta nas populações de risco. Além disso, os dados encontrados contribuem para o desenvolvimento de estratégias para a prevenção e reversão das morbidades metabólicas, através de (re)educação alimentar e utilização de fármacos que auxiliem na melhoria da sensibilidade à insulina, assim como a promoção de intervenções em processos cognitivos relacionados à alimentação, como o treinamento de habilidades executivas que diminuam o consumo excessivo de alimentos hiperpalatáveis (146,147).

É importante ponderar, no entanto, que são necessários estudos adicionais para compreender de forma completa a modulação dos processos cognitivos relacionados à alimentação na RCIU. Por exemplo, é preciso investigar como a atenção e a memória interagem no comportamento alimentar, dado que a atenção às pistas alimentares é maior em obesos e em comedores restritos, possivelmente interferindo na formação de memórias alimentares e gerando o consumo excessivo eventual (152). Considerando isto, o fortalecimento das memórias alimentares, através da evocação das informações da refeição precedente (como tamanho, composição, horário) e da redução de distrações durante as refeições, além do planejamento antecipado do que se servir na refeição subsequente, podem auxiliar os indivíduos nascidos com baixo peso a evitar o consumo alimentar aumentado/hiperpalatável induzido pelas pistas alimentares. Além disso, é necessário integrar o conhecimento dos mecanismos neurobiológicos envolvidos no apetite, na

saciedade, na recompensa, na impulsividade e na interpretação das pistas alimentares para elucidar de forma clara o comportamento alimentar desses indivíduos (31). Do mesmo modo, as alterações de outros mecanismos envolvidos no desenvolvimento da adiposidade e da síndrome metabólica, como a mudança na expressão e sinalização da leptina, da grelina, da colecistoquinina, da adiponectina, do *fat mass and obesity associated gene* ou gene associado à massa gorda e obesidade (112,184–186), devem ser agregadas ao papel da insulina na modulação do comportamento alimentar na RCIU. É importante também incrementar a investigação da sinalização da insulina no hipocampo e em outras regiões corticolímbicas, a fim de esclarecer como este hormônio interfere no controle cognitivo da alimentação nos indivíduos pequenos para a idade gestacional.

Por fim, esta tese apontou evidências do efeito da resistência à insulina nos processos cognitivos relacionados à alimentação, contribuindo para a compreensão do ciclo vicioso para a obesidade em humanos e roedores nascidos com baixo peso. Considerando que as intervenções dietéticas podem ser melhoradas através do conhecimento da neurobiologia do comportamento alimentar (187), os achados deste trabalho contribuem para a elaboração de estratégias específicas de prevenção e reversão das morbidades metabólicas crônicas para essa população vulnerável.

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7. ANEXOS

7.1. CARTA DE APROVAÇÃO DA PESQUISA EXPERIMENTAL

HCPA - HOSPITAL DE CLÍNICAS DE PORTO ALEGRE
GRUPO DE PESQUISA E PÓS-GRADUAÇÃO

COMISSÃO DE ÉTICA NO USO DE ANIMAIS

A Comissão de Ética no Uso de Animais (CEUA/HCPA) analisou o projeto:

Projeto: 130544
Data da Versão do Projeto: 24/03/2014

Pesquisadores:
PATRICIA PELUFO SILVEIRA
AMANDA BRONDANI MUGELLINI

Título: PAPEL DA INSULINA SOBRE A MEMÓRIA E O COMPORTAMENTO ANSIOSO RELACIONADOS AOS ALIMENTOS EM UM MODELO DE RESTRIÇÃO DE CRESCIMENTO INTRAUTERINO EM RATOS

Este projeto foi APROVADO em seus aspectos éticos e metodológicos de acordo com as Diretrizes e Normas Nacionais e Internacionais, especialmente a Lei 11.794 de 08/10/2008, que estabelece procedimentos para o uso científico de animais.

- Os membros da CEUA/HCPA não participaram do processo de avaliação de projetos onde constam como pesquisadores.
- Toda e qualquer alteração do Projeto deverá ser comunicada à CEUA/HCPA.
- O pesquisador deverá apresentar relatórios semestrais de acompanhamento e relatório final ao CEUA/HCPA.

Porto Alegre, 28 de março de 2014.

Profª Irací Lucena da Silva Torres
Coordenadora CEUA/HCPA

7.2. CARTA DE APROVAÇÃO DA PESQUISA CLÍNICA

HCPA - HOSPITAL DE CLÍNICAS DE PORTO ALEGRE
GRUPO DE PESQUISA E PÓS-GRADUAÇÃO

COMISSÃO CIENTÍFICA

A Comissão Científica do Hospital de Clínicas de Porto Alegre analisou o projeto:

Projeto: 120254
Data da Versão do Projeto:

Pesquisadores:
GISELE GUS MANFRO
PATRICIA PELUFO SILVEIRA
GIOVANNI ABRAHAO SALUM JUNIOR
ROBERTA DALLE MOLLE
RAFAELA BEHS JARROS
VERA LUCIA BOSA
ANDRESSA BORTOLUZZI
DIOGO ARAÚJO DE SOUSA
NATAN PEREIRA GOSMANN

Título: Restrição do crescimento intra-uterino e trajetória desenvolvimental de adolescentes e adultos com e sem transtorno de ansiedade: desfechos em saúde mental, nutricional, epigenéticos, biomarcadores e de neuroimagem funcional

Este projeto foi **APROVADO** em seus aspectos éticos, metodológicos, logísticos e financeiros para ser realizado no Hospital de Clínicas de Porto Alegre.
Esta aprovação está baseada nos pareceres dos respectivos Comitês de Ética e do Serviço de Gestão em Pesquisa.

- Os pesquisadores vinculados ao projeto não participaram de qualquer etapa do processo de avaliação de seus projetos.

- O pesquisador deverá apresentar relatórios semestrais de acompanhamento e relatório final ao Grupo de Pesquisa e Pós-Graduação (GPPG)

Porto Alegre, 08 de novembro de 2012.

Profª Nadine Clausell
Coordenadora GPPG

7.3. TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO DA PESQUISA CLÍNICA

DADOS DE IDENTIFICAÇÃO DO PARTICIPANTE DA PESQUISA OU RESPONSÁVEL LEGAL

1. NOME: .....

2. RESPONSÁVEL LEGAL: .....
NATUREZA (grau de parentesco, tutor, curador etc.): .....

DADOS SOBRE A PESQUISA

1. TÍTULO DO PROTOCOLO DE PESQUISA

"Restrição do crescimento intrauterino e trajetória desenvolvimental de adolescentes e adultos com e sem transtorno de ansiedade: desfechos em saúde mental, nutricional, epigenéticos, biomarcadores e de neuroimagem funcional"

2. Pesquisadores responsáveis: Gisele Gus Manfro e Patrícia Pelufo Silveira
CARGO/FUNÇÃO: Professora da Faculdade de Medicina/ Professora da Faculdade de Medicina
UNIDADE: Departamento de Psiquiatria e Medicina Legal da Universidade Federal do Rio Grande do Sul, coordenadora do PROTAIA/ Departamento de Pediatria e Puericultura
Pesquisadores executantes: Andressa Bortoluzzi, Diogo Souza, Giovanni Abrahão Salum Júnior, Rafaela Behs Jarros, Roberta Dalle Molle Rudineia Toazza, Natan Pereira Gosmann
Pesquisadores Colaboradores PUC: Augusto Buchweitz, Alexandre Franco

3. Avaliação do risco da pesquisa: ( ) risco mínimo **(x) risco baixo** ( ) risco médio ( ) risco maior

4. **Duração da pesquisa:** A duração total deste projeto está prevista para 1,5 anos.

5. Justificativa e objetivos

Os transtornos de ansiedade iniciam na infância e podem se manter até a vida adulta. Eles também podem influenciar os diferentes hábitos alimentares. Como é comum a diminuição de crescimento do feto durante a gravidez e isto poderia aumentar a chance do desenvolvimento de doenças do metabolismo e psiquiátricas, estamos estudando como isto ocorre e suas consequências, a fim de propiciar a prevenção e um melhor tratamento dessas doenças. O objetivo desse trabalho é investigar se a restrição de crescimento do feto durante a gestação está associada a alterações no desenvolvimento de adolescentes e adultos com e sem ansiedade investigando: (1) como se iniciam e se mantém os transtornos de ansiedade; (2) como se iniciam e se mantém os diferentes comportamentos alimentares e os indicadores de composição corporal; (3) as modificações na forma como os genes se expressam e (4) o funcionamento cerebral.

6. Procedimentos

<u>Procedimentos para seleção de sujeitos que vão entrar na pesquisa:</u>

Se você **pai e/ou mãe ou responsável (em caso do participante ser menor de 18 anos)** autorizar a participação de seu filho (a) na pesquisa, você e seu filho (a) serão convidados a participar de:

Observação: Embora os pais participem dessa avaliação, no caso de crianças pequenas, acompanhando seu filho e ajudando a responder alguns questionários sobre os sentimentos e hábitos alimentares, achamos importante lembrar que todas as fases de avaliação serão para chegarmos ao diagnóstico dos sintomas que o **participante do estudo apresenta** e não referente ao diagnóstico dos pais.

(1) Avaliação diagnóstica psiquiátrica, com duração de 1h30min. Nesta avaliação, vocês irão preencher alguns questionários sobre os próprios sentimentos e comportamentos no dia-a-dia e a forma como sua família se relaciona. É possível que vocês se sintam cansados e constrangidos por ter que responder tantos questionários sobre suas emoções.

(2) Avaliação Neuropsicológica. Nesta avaliação, será feita algumas atividades como contar números e completar figuras, ou seja, atividades escolares comuns.

(3) Avaliação Nutricional. Nesta avaliação, será feita uma avaliação das medidas do corpo, ou seja, peso, altura, avaliação do comportamento alimentar e do nível de atividade física do seu filho, através de perguntas sobre os hábitos alimentares dele e suas atividades diárias.

(4) Será feita uma coleta de saliva para avaliar possíveis marcadores dos genes do seu filho (a) que possam ter alguma associação com os transtornos de ansiedade.

(5) Avaliação do funcionamento do cérebro através de uma máquina de ressonância magnética funcional onde seu filho (a) ficará por aproximadamente 40 minutos dentro dela e realizará algumas tarefas simples como responder a algumas perguntas ou ouvir algumas histórias. Esse exame será realizado na PUCRS (Pontifícia Universidade Católica do Rio Grande do Sul, Av. Ipiranga, 6681 - Partenon - Porto Alegre/RS) e informará como algumas áreas do seu cérebro funcionam.

7. Riscos e inconveniências

Haverá acompanhamento dos pesquisadores em todas as etapas do projeto e dos seus procedimentos, porém lembramos que as tarefas a serem realizadas para a conclusão deste projeto possuem alguns riscos e/ou inconveniências para o participante: você e seu filho (a) poderão ficar cansados com o preenchimento dos questionários, já que são vários. Também podem se sentir ansiosos ou constrangidos por responder perguntas sobre seus próprios sentimentos e comportamentos no dia-a-dia, pois os conteúdos envolvem emoções, hábitos alimentares e de atividade física que podem ser desagradáveis. Tentaremos minimizar estes possíveis efeitos utilizando avaliadores treinados e instrumentos curtos. O exame do funcionamento do cérebro é um exame pelo qual não são conhecidos riscos para os participantes, porém é um pouco barulhento, o que pode fazer com que seu filho (a) se incomode com os ruídos e se sinta desconfortável em ficar deitado durante todo o tempo do exame. Vocês terão que se deslocar de sua casa por duas ou três vezes para que as coletas e o exame possam ser feitos.

8. Potenciais benefícios

Embora os resultados desta pesquisa possam não ajudar seu filho (a) diretamente, vocês terão uma avaliação clínica sobre diagnóstico em psiquiatria e uma avaliação neuropsicológica ou seja, as táticas que o cérebro dele (a) usa para resolver algumas tarefas; maior conhecimento acerca dos transtornos de ansiedade na infância e adolescência o que poderá ajudar no entendimento sobre a doença; maior conhecimento acerca do consumo alimentar do seu filho (a), bem como a composição corporal; e um exame de imagem sobre como o cérebro dele funciona durante a realização de algumas tarefas.

Gostaríamos ainda de deixá-lo ciente dos seguintes direitos que seu filho (a) terá:

a) **Garantia do uso dos dados colhidos apenas para a finalidade especificada nesse estudo:** Os dados obtidos somente serão usados para o fim previsto neste projeto de pesquisa e qualquer outro uso terá que se solicitar a sua autorização.
b) **Sigilo e privacidade:** As informações produzidas nesta tarefa serão mantidas em lugar seguro, com códigos e a identificação só poderá ser realizada pelo pessoal envolvido diretamente com o projeto. Caso o material venha a ser utilizado para publicação científica ou atividades didáticas, não serão utilizados nomes que possam vir a identificá-lo.
c) **Direito à informação**: Em qualquer momento do estudo você poderá obter mais informações com a Prof. Dra. **Gisele Gus Manfro** e/ou Prof. Dra. **Patrícia Pelufo** pelo telefone (0xx51) 3358-8983 ou (0xx51) 3359-8019, que estarão aptas a solucionar suas dúvidas. Você poderá solicitar informações de qualquer conhecimento significativo descoberto durante este projeto.
d) **Direito de informação sobre aspectos éticos da pesquisa:** Se você tiver alguma consideração ou dúvida sobre a ética da pesquisa, entre em contato com o Comitê de Ética em Pesquisa (CEP) – localizado no Hospital de Clínicas, no 2º andar, sala 2227, com horário de atendimento das 8h às 17h, Fone/Fax: (0xx51) 3359-7640
e) **Despesas e compensações**: Não há despesas pessoais, ou seja, não será cobrado nada a você em qualquer fase do estudo, incluindo exames e consultas. Também não há compensação financeira ou qualquer tipo de pagamento relacionado à sua participação. Se existir qualquer despesa adicional, ela será custeada pelo orçamento da pesquisa. Em caso de dano pessoal, diretamente causado pelos procedimentos ou tratamentos propostos neste estudo (nexo causal comprovado), você tem direito a tratamento médico na Instituição, bem como às indenizações legalmente estabelecidas.
f) **Direito a não participar ou interromper sua participação no estudo**: Você tem liberdade para se recusar a participar ou retirar seu consentimento, em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado ou do seu filho (a).
g) **Garantia de assistência e de continuidade do tratamento:** Seu filho (a) será devidamente acompanhado e assistido durante todo o período de sua participação no projeto, bem como será encaminhado para a rede de assistência a saúde na ocasião de necessidade de cuidados adicionais.

Acredito ter sido suficientemente informado a respeito das informações que li ou que foram lidas para mim, descrevendo o estudo: "Restrição do crescimento intrauterino e trajetória desenvolvimental de adolescentes e adultos com e sem transtorno de ansiedade: desfechos em saúde mental, nutricional, epigenéticos, biomarcadores e de neuroimagem funcional"

Eu discuti com o pesquisador (a) sobre a minha decisão em autorizar meu filho (a) participar desse estudo. Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem realizados, seus desconfortos e riscos, as garantias de confidencialidade e de esclarecimentos permanentes. Ficou claro também que a participação do meu filho (a) é isenta de despesas e terá garantia do acesso a tratamento hospitalar quando necessário. Concordo voluntariamente na minha participação do meu filho (a) e poderei retirar o meu consentimento a qualquer momento, antes ou durante o mesmo, sem penalidades ou prejuízo ou perda de qualquer benefício que eu possa ter adquirido, ou no meu atendimento neste Serviço.

Nome do participante:_____

_____ Data ____/___/___
Assinatura do (a) participante (em caso de maiores de 18 anos ou se a criança mesma puder fazê-la)

Nome do (a) representante legal:_____
_____ Data ___/___/___
Assinatura do (a) representante legal

Para casos de pacientes menores de 18 anos, analfabetos, semianalfabetos ou portadores de deficiência auditiva ou visual.

Nome do pesquisador (a):_____

_____
Assinatura do pesquisador (a) Data ___/___/___

(Somente para o responsável do projeto)
Declaro que obtive de forma apropriada e voluntária o Consentimento Livre e Esclarecido deste paciente ou representante legal para a participação neste estudo.

Este Termo de Consentimento Livre e Esclarecido (TCLE) é elaborado em duas vias, uma via fica com o participante e a outra com o pesquisador (a).

7.4. PRODUÇÃO CIENTÍFICA

Artigos publicados

1. Rodrigues, D. M.; Reis, R. S.; Molle, R. D.; Machado, T. D.; Mucellini, A. B.; Bortoluzzi, A.; Toazza, R.; Perez, J. A.; Salum, G. A.; Agranonik, M.; Minuzzi, L.; Levitan, R. D.; Buchweitz, A.; Franco, A. R.; Manfro, G. G.; Silveira, P. P. *Decreased comfort food intake and allostatic load in adolescents carrying the A3669G variant of the glucocorticoid receptor gene.* **Appetite**, p. 21-28, 2017. Fator de impacto: 3.403

2. Mucellini, A. B.; Fonseca, N. K. O.; Manfro, G. G.; Silveira, P. P. *Hippocampal insulin resistance and altered food decision-making as players on obesity risk.* ***Neuroscience and Biobehavioral Reviews***, 2017. Fator de impacto: 8.299

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7.5. PRÊMIOS CIENTÍFICOS

Honor David Barker Award

Melhor apresentação oral – Mucellini, A. B.; Molle, R. D.; Rodrigues, D. M.; Reis, R. S.; Machado, T. D.; Bortoluzzi, A.; Toazza, R.; Salum, G. A.; Manfro, G. G.; Silveira, P.P. *Low birth weight is associated with impairment of memory related to food in adolescents*. **IV International Symposium on Metabolic Programming and Stress & I Meeting of Ibero-American DOHaD Chapter, 2014**, Ponta Grossa.

4th INTERNATIONAL SYMPOSIUM ON METABOLIC PROGRAMMING AND STRESS

&

1st MEETING OF IBERO-AMERICAN DOHaD CHAPTER
DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

Certificate of Participation

We certify that **Amanda Brondani Mucellini** won the *Honor David Barker Award* (Short Communication) in the 4th International Symposium on Metabolic Programming and Stress and 1st Meeting of Ibero-American DOHaD Chapter - Developmental Origins of Health and Disease, held from November 13th until November 16th, Ponta Grossa, Brazil.

Ponta Grossa, **November 16th**, 2014.

Paulo C.F. Mathias

Prêmio Ciência nos Primeiros 1000 dias

Segundo melhor trabalho de pesquisa avançada – Laureano, D. P.; Alves, M. B.; Miguel, P. M.; Machado, T. D.; Reis, A. R.; Mucellini, A. B.; Silva, F. C.; Molle, R. D.; Desai, M.; Ross, M. G.; Silveira, P.P. *Nascer pequeno modifica a resposta ao alimento doce - estudo da via dopaminérgica*. **II Prêmio Ciência nos Primeiros 1000 dias**, 2016, São Paulo.