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Preclinical assessment of leptin transport into the cerebrospinal fluid in diet-induced obese minipigs

Chmielewski A, Hubert T, Descamps A, et al (2019) Obesity [1]

Objective: A minipig model was employed to explore the changes in endogenous leptin transport into the central nervous system and in hypothalamic sensitivity to exogenous leptin when individuals are placed on high-fat diet (HFD) compared with standard diet.

Methods: Serum and cerebrospinal fluid (CSF) leptin concentrations during 10 weeks of HFD versus standard diet and exogenous leptin-induced STAT3 phosphorylation in the hypothalamus of minipigs were assessed, and the hypothalamic leptin-sensitive cells were characterized by immunofluorescence.

Results: The efficiency of the passage of endogenous blood-borne leptin into the CSF (measured as the log [CSF: serum leptin ratio]) decreased over time in minipigs fed a HFD ($\beta = -0.04 \pm 0.005$ per kilogram of weight gain in HFD; $P < 0.0001$), while it remained stable in minipigs fed a standard diet. However, the ability of peripherally administered leptin to activate its receptor in hypothalamic neurons was preserved in obese minipigs at 10 weeks of HFD.

Conclusions: Together, these data are consistent with the existence of an early-onset transport deficiency for

endogenous circulating leptin into the brain in individuals developing obesity, preceding the acquisition of hypothalamic leptin resistance. Although additional studies are required to identify the underlying mechanisms, our study paves the way for the development of new preclinical pharmacological models targeting the restoration of the shuttling of peripheral leptin into the central nervous system to manage obesity.

Commentaires : L'utilisation des miniporcs comme modèle animal d'obésité demeure particulièrement pertinente dans la mesure où ces animaux nous sont très proches en matière d'anatomie, de physiologie, de répartition adipeuse intra-abdominale, voire même de comportement alimentaire. Dans cette étude, c'est le phénomène de leptinorésistance, et sa genèse en fonction de la prise de poids, qui est testé. C'est ce mécanisme qui empêche la leptine d'actionner au niveau de l'hypothalamus les voies anorexigènes chez des modèles murins et dans certains cas chez l'homme. Ces miniporcs devenus obèses, mis au régime high-fat, comparés à d'autres restés normopondéraux en régime classique, développent un défaut de passage de la leptine endogène via la barrière hématoencéphalique jusqu'au niveau du liquide céphalorachidien. De plus, cette résistance de transport apparaît avant toute anomalie métabolique. Ainsi, la leptinorésistance pourrait devenir une cible thérapeutique. D'autres études notamment translationnelles sur l'homme sont requises. Certaines sont déjà en cours...

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Taste loss with obesity in mice and men

Kaufman A, Kim J, Noel C, et al (2019) Int J Obes [2]

Background: Our sense of taste is critical in defining our food choices and habits. Located primarily in our tongue, taste buds are small assemblies of constantly renewing sensory cells, tasked with evaluating oral stimuli before the food we eat is consumed.

Methods: Using both mice and a free-living human population, we tracked taste papilla abundance with weight gain, to test for deficiencies in the taste system of obese mice and humans with increased adiposity.

Results: Mice fed a high-fat diet for 8 weeks expressed markers for all subtypes of taste cells at a lower level than chow-fed counterparts. This came alongside the loss of markers for taste cell proliferation (Ki-67) and development (β -catenin), as well as lower fungiform papillae density, consistent with earlier results showing lower circumvallate taste bud abundance in obese mice. Likewise, in a population of college students tracked through 4 years of college attendance, the change in density of fungiform papillae, which house taste buds in the anterior tongue, was negatively correlated with change in neck circumference, a marker of adiposity.

Conclusions: These results highlight changes in taste during weight gain as a potentially important consideration in the study of obesity.

Commentaires : Les récepteurs du goût sont localisés sur des cellules épithéliales spécialisées, regroupées au sein de bourgeons gustatifs situés sur la langue. Les auteurs confirment ici, sur des modèles murins, que les marqueurs génétiques de ces récepteurs sont sous-représentés chez les souris obèses par rapport aux souris de poids normal. De plus, ces cellules spécialisées se renouvellent et prolifèrent moins chez les souris obèses... Chez l'homme et dans une cohorte prospective d'étudiants, les auteurs retrouvent une corrélation inversée entre adiposité et densité de papilles gustatives sur la langue. Ce constat confirme donc sur le plan macroscopique ce que d'autres auteurs avaient déjà mis en évidence, à savoir une diminution de l'intensité et de la perception du goût chez des individus à IMC et adiposité plus importants. Cette piste reste intéressante sur l'étiologie ou la pérennisation du surpoids, par exemple si l'on considère que ces récepteurs participent au phénomène de rassasiement sensoriel spécifique encore appelé alliesthésie.

Oral contraceptives use and development of obesity in a Mediterranean cohort: the SUN (Seguimiento Universidad de Navarra) Project

San-Juan-Rodriguez A, Martín-Moreno JM, Bes-Rastrollo M, et al (2019) Int J Obes [3]

Background: The use of oral contraceptives (OC) has been suggested to represent a potential risk factor for the development of obesity. However, the available literature assessing the relationship between OC use and the development of obesity is still scarce and characterised by controversial heterogeneity. We prospectively evaluated the association between the use of OC and the development of obesity in female participants of a middle-aged and free-living cohort.

Methods: The study population included 4,920 female Spanish university graduates, initially non-obese women, with mean age (standard deviation) 28.2 (5.4) years. The study population was followed up for a mean of 8.6 (3.7) years. Self-reported use of OC and body mass index were assessed at baseline and biennially during follow-up. We used generalized estimating equation models to evaluate the association between exposure to OC and the development of obesity.

Results: After adjusting for potential confounders, baseline OC use was associated with higher odds of new-onset obesity during the full follow-up period (multi-variable-adjusted odds ratio [OR] = 1.78; 95% Confidence Interval [CI]: 1.01–3.15). The continued use of OC for periods of time longer than 2 years was significantly associated with a higher risk of developing obesity (OR = 2.82, 95% CI: 1.17–6.82).

Conclusions: According to our prospective cohort study, OC use is significantly associated with higher odds of obesity development, especially when the use of OC is steady and extends over periods of more than 2 years.

Commentaires : Nous pouvons souvent constater une attribution externe des causes de prise de poids chez nos patients, parfois farfelues, ou l'iatrogénie de tel ou tel traitement, avec en tête de liste les psychotropes et les « hormones ». Bien entendu, ces traitements peuvent influencer le métabolisme et le comportement alimentaire à l'origine donc de variations pondérales. Le cas de la contraception estroprogestative (CE) demeurant jusqu'à présent peu connu, les auteurs ont suivi en prospectif sur plusieurs années 4 920 femmes débutant ce type de traitement. C'est la première fois qu'une étude de cette envergure met en évidence un lien entre développement de l'obésité et CE après ajustement sur diverses variables. Cette corrélation est surtout marquée pour des durées de traitement supérieures à deux ans. Cette donnée est donc à prendre en compte en cas de prise de poids inexplicée.

Attribution of weight regain to emotional reasons amongst European adults with overweight and obesity who regained weight following a weight loss attempt

Sainsbury K, Evans EH, Pedersen S, et al (2019) Eat Weight Disord [4]

Purpose: Despite the wide availability of effective weight loss programmes, maintenance of weight loss remains challenging. Difficulties in emotion regulation are associated with binge eating and may represent one barrier to long-term intervention effectiveness in obesity. The purpose of this

study was to determine the relationship between emotion regulation difficulties and the extent of weight regain in a sample of adults who had lost, and then regained, weight, and to examine the characteristics associated with emotional difficulties.

Methods: Two thousands adults from three European countries (UK, Portugal, and Denmark) completed an online survey assessing self-reported weight loss and regain following their most recent weight loss attempt. They also completed a binge eating disorder screening questionnaire and, if they had regained weight, were asked if they attributed it to any emotional factors (a proxy for emotion regulation difficulties). Spearman's correlations and logistic regression were used to assess the associations between emotion regulation, weight regain, and strategy use.

Results: Emotion regulation difficulties were associated with greater weight regain ($N = 1,594$ who lost and regained weight). Attribution to emotional reasons was associated with younger age, female gender, loss of control and binge eating, lower perceptions of success at maintenance, using more dietary and self-regulatory strategies in weight loss, and fewer dietary strategies in maintenance.

Conclusions: Weight-related emotion regulation difficulties are common amongst regainers and are associated with regaining more weight. Affected individuals are already making frequent use of behavioural strategies during weight loss, but do not apply these consistently beyond active attempts. Simply encouraging the use of more numerous strategies, without concurrently teaching emotion regulation skills, may not be an effective means to improving weight outcomes in this group.

Commentaires : Cette étude portant sur des adultes de différents pays européens ayant entrepris de perdre du poids met en évidence l'importance des difficultés de régulation émotionnelle sur la reprise pondérale. Cette étude identifie que les patients rapportant avoir repris du poids en lien avec l'alimentation émotionnelle reprennent plus de poids que les patients ne rapportant pas de cause émotionnelle à leur reprise pondérale. Cette étude met en évidence des facteurs de risque à la fois démographiques (être une femme, jeune), pondéraux (avoir un IMC de départ élevé) et psychologiques (plus faible sentiment d'autoefficacité, perte de contrôle alimentaire, binge eating disorder, nombre important de tentatives de perte de poids). L'intérêt de cette étude en population générale réside aussi dans la confirmation, sur un panel très large, de l'effet délétère de la restriction. En effet, on ne peut que constater que les facteurs favorisant la reprise de poids pour des raisons émotionnelles sont des facteurs ayant été identifiés comme favorisés eux-mêmes par les régimes. À l'heure où les prescriptions diététiques sont encore légion, on ne peut que constater les dégâts que ceux-ci ont créés... et créeront encore ?

Why are you eating, mom? Maternal emotional, restrained, and external eating explaining children's eating styles

Zarychta K, Kulis E, Gan Y, et al (2019) *Appetite* [5]

This study investigated if three maternal eating styles (emotional eating style, external eating style, and restrained eating style) predict respective eating styles in children. In particular, we tested if these associations are different in mother–daughter dyads, compared to mother–son dyads. Data were collected twice, at the baseline (Time 1; T1) and at the 10-month follow-up (Time 2; T2), with $N = 822$ mother–child dyads participating at T1. Children (55% girls, 5–12 years old, $M = 8.21$, $SD = 1.40$) were interviewed; mothers (aged 23–59 years old, $M = 35.93$, $SD = 5.24$) completed the questionnaire assessing their eating styles. Participants' weight and height were measured objectively. Path analysis, accounting for dyadic interdependency and autocorrelations, was applied. In mother–daughter dyads, maternal emotional eating (T1) predicted daughters' emotional eating (T2) whereas maternal restrained eating (T1) predicted daughters' restrained eating (T2). There were no effects of external eating in mother–daughter dyads. A different pattern of associations was found for mother–son dyads, with maternal emotional eating (T1) and external eating (T1) predicting sons' emotional eating (T2) and external eating (T2), respectively. There was no effect of maternal restrained eating in mother–son dyads. Maternal eating styles explain child's eating styles with distinct effects depending on child's sex. Educating mothers about the effects of their own eating styles on daughters' and sons' eating styles might be useful to promote adequate responses to hunger and satiety signals.

Commentaires : L'influence du comportement alimentaire des mères sur le comportement alimentaire des jeunes filles est maintenant bien étayée. Cette étude s'attache à étudier si un même style de comportement alimentaire maternel pourrait avoir des conséquences différentes en fonction du sexe de l'enfant. De fait, si l'alimentation émotionnelle maternelle influence l'alimentation émotionnelle chez l'enfant indépendamment de son sexe, un style alimentaire restrictif impacte la restriction alimentaire des petites filles uniquement. Il en va de même pour l'alimentation externe maternelle qui entraîne un style alimentaire externe chez les jeunes garçons, mais pas les jeunes filles. Cette variabilité en fonction du sexe de l'enfant face à un même style de comportement alimentaire maternel apporte un nouvel éclairage en termes de prise en charge, mais surtout de prévention spécifique des troubles du comportement alimentaire chez l'enfant.

Overweight adults are more impulsive than normal weight adults: evidence from ERPs during a chocolate-related delayed discounting task

Liu Y, Zhao J, Zhang X, et al (2019) *Neuropsychologia* [6]

Overweight or obesity can be accompanied by abnormalities in executive function and related neural markers. The aim of the present study was to investigate the behavioral and neural correlates of food-related decision-making in overweight and normal-weight adults. We used a Delayed Discounting Task (DDT), which requires participants to choose between smaller immediate rewards and larger delayed rewards. In total, 24 overweight adults and 24 normal-weight adults participated; all participants engaged with a food-related DDT, and their responses were measured using event-related potentials (ERPs). In the current study, we take the area under the curve (AUC), number of smaller immediate rewards, and reaction times (RTs) as behavioral indicators of DDT. AUC is an individual's discounting rate, with smaller AUC reflecting more impulsive decision-making. Number of smaller immediate rewards also reflects impulsivity. For ERPs, N2, reward-related positivity, P3, and late positive component (LPC) were investigated. Behavioral results showed smaller AUC, more choice of smaller immediate rewards, and longer RTs in overweight adults than in normal-weight adults. Neural markers showed that overweight adults elicited greater N2 in larger delayed rewards than in smaller immediate rewards and also elicited greater reward-related positivity than normal-weight adults. Moreover, the P3 and LPC mean amplitudes of overweight adults were greater than those of normal-weight adults. Pearson correlation analysis showed that body mass index (BMI) was positively related to P3 and LPC, while AUC was negatively related to P3. The findings thus suggest that overweight adults are more impulsive than normal-weight adults. Moreover, overweight adults might experience more cognitive conflict before their reaction, and they might allocate more cognitive resources to food-related stimuli and might have higher-order cognitive processes more involved in motivation or emotion regarding food-related stimuli. This is the first study investigating ERP correlates

of food-related decision-making in overweight adults, and it enriches the theoretical models by providing neural markers for future study.

Commentaires : *Cette étude met en évidence, à l'aide d'une méthodologie de « récompense différée », une différence d'impulsivité entre un groupe de patients en surpoids et un groupe de patients normopondéraux. En effet, les patients en surpoids choisissent plus facilement des récompenses inférieures en termes de volume de chocolat, mais fournies sans délai. De plus, le temps de décision nécessaire est augmenté dans le groupe « surpoids » comparativement au groupe « poids normal », illustrant un conflit cognitif plus grand chez les patients en surpoids dans le cadre d'une prise de décision alimentaire (à restriction cognitive identique). Cette étude vient confirmer les résultats obtenus concernant l'impulsivité des patients en surpoids de manière générale, mais apporte la preuve scientifique que cette impulsivité serait encore plus notable lorsque le patient doit faire un choix en rapport avec l'alimentation. Cette étude vient renforcer l'intérêt croissant pour la variable impulsivité dans la prise en charge des patients et des prises en charge visant à diminuer la sensibilité de nos patients aux stimuli alimentaires.*

Références

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