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EARNEST

EARly Nutrition programming- long term follow up of Efficacy and Safety Trials and integrated epidemiological, genetic, animal, consumer and economic research

Instrument: Integrated Project

Thematic Priority 5.4.3.1: Food Quality and Safety

Final public report on activity 3.3.5:

Programming of glucose intolerance and obesity by different dietary composition during the weaning period in the rat

Period covered from 15.04.2005 to 14.10.2010

Start date of project: 15.04.2005 Duration: 5,5 Years

Organisation Name of Lead Contractor for this report: Nestlé

Activity objectives

- To investigate the programming potential of fat/carbohydrate content of weaning diet on later development of obesity and glucose homeostasis (1).

- To choose a sensitive and practical IUGR rat model for nutritional studies, aimed at investigating the link between low birth weight, early post-natal catch-up growth and later development of obesity and glucose intolerance (2).

1 Programming impact of fat-to-carbohydrate content of weaning diet on later susceptibility to obesity and glucose homeostasis tin rats

The increasing pandemic of obesity and a lack of an effective treatment have driven research interests further towards preventative therapy, especially during early life when metabolic processes may be defined or reset. The prenatal and suckling periods are now recognized as critical windows for early programming of adult metabolic disease (Desia M et al 2007). By contrast, whether or not programming may also occur during the period of complementary feeding (weaning) is unclear. Dietary fat intake, which is high during suckling, is markedly reduced during weaning because of partial replacement of high fat milk by carbohydrate (CHO)-rich complementary foods such as fruits, vegetables, weaning cereals, fruit juices etc (Lapinleimu H et al 1995; Capdevila F et al 1998). During this transition from suckling to complementary feeding, many important hormonal and enzymatic changes occurs such as an increase in plasma insulin and increase of *de novo* lipogenesis, that affect CHO and lipid metabolism (Girard J et al 1992). Whether earlier initiation of these hormonal and metabolic changes, can have a long-lasting impact on later health is not known.

In this study, we have investigated, the extent to which alterations in the fat and CHO content of the weaning diet may influence the later development of obesity and impact upon whole-body insulin sensitivity, in the rats.

Three groups of male rats (24/group) were fed from 2 to 5 wks (phase I) on weaning diets varying in their fat/CHO energy ratios, namely: 10/70 low-fat, high-CHO (LFHC); 30/50 medium-fat, medium-CHO (MFMC) and 60/30 high-fat, high-CHO (HFHC). After weaning period, all animals were fed ad-libitum, first on a low-fat chow diet (13% fat E) for 30 wks (phase II), and subsequently on a high-fat diet (45% fat E) for another 18 wks (phase III).

At the end of weaning period (phase I), the group fed with the HFLC diet demonstrated higher plasma glucose and insulin responses to an OGTT ($P<0.05$). However, this effect was transient and did not persist into adulthood (phases II and III). By contrast, when challenged with a high-fat diet later in life (age 35-52 wks), the group previously fed with the LFHC diet showed greater gains in body weight and body fat (absolute and % wt) than those fed with the diets higher in fat ($p<0.05$ for all except wt gain between LFHC vs. HFLC; $p=0.07$).

These results suggest that the composition of the weaning diet (fat/CHO content) plays a role in an individual's susceptibility to developing adiposity later in life. A low-fat weaning diet appears to increase ones susceptibility to developing adiposity later in life if an unfavourable diet, such as a high-fat diet is consumed. The mechanism of action is not clear but does not seem to be associated with lower basal or insulin responses to a glucose challenge.

In conclusion, these results (Shahkhalili Y, et al submitted) provide evidence, for the first time, that metabolic programming can occur during the weaning period, and emphasizes the importance of the fat/CHO content of the complementary diet and its relation to susceptibility of developing adiposity later in life. Our results, if relevant to infants, are in line with the current dietary recommendations specifying that the fat intake should not be restricted until 2 years of age (Olson RE et al 1995).

2 Comparison of two models of intrauterine growth restriction (IUGR) for early catch-up growth and later development of glucose intolerance and obesity in rats.

Intrauterine growth restriction (IUGR), resulting in reduced birth weight and subsequent rapid catch up growth, are considered as risk factors for later development of chronic non-communicable, metabolic diseases (Barker DJP et al 1993; Hales CN et al 1991; Bieswal F et al 2006). To investigate the mechanisms by which IUGR predisposes to later development of metabolic diseases, different animal models have been developed and widely used during the last two decades, in particular those based upon, prenatal food or protein restriction and exposure to specific hormones during gestation (Haugaard CT et al 2001) However, although these IUGR models are commonly used in research, a direct comparison between these models pertaining to the link between small birth weights, the kinetics of catch-up growth and development of obesity and glucose intolerance is still lacking.

In this study, we have directly compared these two rat models of IUGR; maternal food restriction (FR) and dexamethasone exposure (DEX) for early catch-up growth and later development of glucose intolerance and obesity in Sprague-Dawley rats.
Mated dams were randomly divided into three groups at 10 days gestational age. Group FR was food restricted (50% of non-gestating rats) during the last 11 days of gestation; Group DEX received dexamethasone injections during the last week of gestation and Group CON, the control group, had no intervention. Birth weight, catch-up growth, body weight and food intake were measured in male offspring for 22 weeks. Body composition, blood glucose and plasma insulin in response to a glucose load were assessed at 8, 16 and 22 weeks.

Pups from both FR and DEX dams had similarly lower birth weights than CON (23-25%, $p<0.0001$), but catch-up growth- which occurred during the suckling period – was much more rapid in FR than DEX offspring (6 vs. 25 days, 95%CI). Post-weaning, there were no significant differences between-group in food intake, body weight, body fat and plasma

insulin, but baseline plasma glucose at 22 weeks and 2-h glucose area-under-the-curve (AUC) at 8 and 22 weeks were greater only in FR vs. CON offspring ($P<0.05$), thereby contrasting with the lack of significant differences between DEX vs. CON.

These results suggest that prenatal food restriction is a more sensitive model than dexamethasone exposure for studies aimed at investigating the link between low birth weight, early post-natal catch-up growth and later development of glucose intolerance (Shahkhalili Y, et al., 2010).