Social environment and nutritional programming in rodents

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Several preclinical studies have been conducted in which the effects of a postnatal diet with altered lipid structure (i.e. Nuturis®) on short term and later in life health outcomes were investigated of which one is described in Chapter 3 of this thesis. Two comparable mice studies were performed in which metabolic development and the programming capacity of a postnatal diet with Nuturis® on later in life vulnerability to diet induced obesity were investigated. These studies used a similar experimental design and diet intervention as described before (see figure 1 for experimental design) (1). These particular studies were performed with two years in between and due to a move of animal facilities, the experiments were performed at different locations, though with the same staff and similar routine and environmental conditions following protocol standards (2). An important difference between the studies was, however, that the mice were housed socially (n=2 siblings/cage) with a shelter as cage enrichment in the first study while individual housing (n=1/cage) with a plastic tube as enrichment was applied in the second study. In both studies mice were housed in MAC3 cages with similar bedding (aspen wood shavings) and nest material (nestlet) from weaning onwards.

When examining the weight gain of the mice from weaning until P42, it became clear that mice that were individually housed experienced reduced growth rates compared to mice housed in pairs, see figure 2. Exposure of control animals (CTR) to a Western Style Diet (WSD) from P42 onwards increased weight gain and fat (%) accumulation compared to animals fed rodent chow (AIN) in both experiments, see CTR-WSD vs CTR-AIN groups in figure 3A and 3B, although the weight gain and fat accumulation were much higher in individually housed animals in general. In addition, the WSD diet cause hyperphagia only in the individually housed mice, see figure 4A. These results suggest a higher caloric efficiency during WSD exposure and under individual housing conditions. Exposure to Nuturis® diet (NUT) early in life reduced body fat accumulation when fed WSD during adulthood, but this effect was only statistically significant in the mice that were housed in pairs, see CTR-WSD vs NUT-WSD groups in figure 3B. Indeed, a lower caloric efficiency by early life Nuturis® exposure was observed only in pair housed mice; see CTR-WSD vs NUT-WSD groups in figure 4B. An important consideration suggested by these data is the fact that the animals that were kept under individual housing conditions from weaning onwards appeared to be more prone to become obese in adulthood and that effects seem to be exacerbated by WSD exposure. It is not clear whether the excess body fat accumulation observed during adulthood in the individual housed animals may overrule more subtle programming effects by the juvenile diet on later adiposity, or that isolation induced metabolic changes that took place during adolescence modulated diet induced alterations in the developmental trajectories of adipose tissue (WAT) and metabolic function in that period. Altogether, these data suggest that compared to social housing, individual rearing in may induce differences in metabolic programming and may interact with the programming ability of dietary lipid quality early in life in mice.
Figure 1. Two experiments with similar design to investigate the effects of early life Nuturis® diet (NUT) and adult Western Style Diet (WSD) exposure on weight gain and adult body composition development. In experiment 1, male mice were housed socially from weaning onwards whereas in experiment 2 the animals were housed individually.

Figure 2. Body weight gain from weaning to P42 of male mice subjected to diet with Control (CTR) or Nuturis® (NUT) diet in either social housing conditions or individual housing from weaning onwards. Data represent mean+SEM, n=10-12/group.
Figure 3. Accumulation of A body weight, and B body fat % between P42 and 98 of male mice, that were subjected to either Nuturis® diet between P16 and 42 and subjected thereafter to WSD, or that were subjected to CTR-IMF diet between P16 and 42 and subjected thereafter to WSD or AIN, in either social housing conditions or individual housing from weaning onwards. Data represent mean+SEM; n=10-12/group; * p<0.05; # 0.05<p<0.1.

Figure 4. A Average daily food intake and, B caloric efficiency between P42 and 98 of male mice, that were subjected to either Nuturis® diet between P16 and 42 and subjected thereafter to WSD, or that were subjected to CTR-IMF diet between P16 and 42 and subjected thereafter to WSD or AIN, in either social housing conditions or individual housing from weaning onwards. Data represent mean+SEM; n=6/group for social housing experiment, 10/group for individual housing experiment; * p<0.05; # 0.05<p<0.1.
There are several mechanisms that may theoretically contribute to the observed differences. Next to the nutritional environment early in life, the social environment and exposure to psychosocial stressors are environmental factors that are known to impact health of individuals. For social species such as rodents, the social isolation that comes with single housing may cause chronic stress (3, 4) which has been shown to lead to a variety of neurochemical changes leading to impaired cognitive function and altered anxiety and depression-like behaviours (5-7). Due to critical steps in brain and endocrine development that take place in the period between weaning and sexual maturation, adolescence in rodents represents a period of heightened vulnerability to social isolation stress (8). It is well known that also social isolation after weaning induces permanent abnormalities in brain structure and cognitive and behavioural functioning in rodents (9-11).

Secondly, single housing may affect energy balance regulation via alterations in homeostatic (i.e. lack of social thermoregulation (12), and hedonic mechanisms (stress-induced changes in functioning of higher brain area’s involved in food intake regulation such as the reward system (13)), as well as via stress-induced alterations in circulating glucocorticoid levels directly affecting the CNS-adipose tissue axis (14-16). These isolation induced alterations in body weight and metabolic health status could also influence the sensitivity and/or response of the individual to other environmental factors such as diet. Indeed, 3 weeks of social isolation reduced body weight and body fat accumulation in male mice on a normal diet but increased the sensitivity to diet-induced obesity (17). In another study, eight weeks of social isolation resulted in higher adiposity while on normal diet (18). Of note, in the aforementioned studies the social isolation commenced during adulthood (i.e. 12 weeks of age), when mice were metabolically fully mature.

Similar to isolation induced changes in brain development and functioning, the consequences of isolation induced changes in energy balance regulation on body weight and metabolic phenotype of an individual may depend on the timing and duration of the isolation. Adolescence is a period of rapid lean body growth (19, 20) and adipose tissue development (21, 22), and alterations in energy balance regulation during this period may affect growth and metabolic development, which in turn may change later life susceptibility to metabolic disease. Due to shared neuroendocrine pathways and targets, social stress during adolescence may modulate the sensitivity of the individual to nutritional programming of metabolic and/or mental health. Moreover, a possible interaction between effects of diet and social housing situation on metabolic programming and cognitive and behavioural outcomes during adolescence and adulthood cannot be excluded. The effects of social housing status, and its potential interaction with effects of early life diet on brain development and metabolic programming will be further investigated in follow-up studies.
References


