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Impairment of hippocampal-dependent memory induced by juvenile high-fat diet intake is associated with enhanced hippocampal inflammation in rats

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ABSTRACT

In addition to metabolic and cardiovascular disorders, obesity pandemic is associated with chronic low-grade inflammation as well as adverse cognitive outcomes. However, the existence of critical periods of development that differ in terms of sensitivity to the effects of diet-induced obesity remains unexplored. Using short exposure to a high-fat diet (HFD) exerting no effects when given to adult mice, we recently found impairment of hippocampal-dependent memory and plasticity after similar HFD exposure encompassing adolescence (from weaning to adulthood) showing the vulnerability of the juvenile period (Boitard et al., 2012). Given that inflammatory processes modulate hippocampal functions, we evaluated in rats whether the detrimental effect of juvenile HFD (jHFD) on hippocampal-dependent memory is associated with over-expression of hippocampal pro-inflammatory cytokines.

jHFD exposure impaired long-term spatial reference memory in the Morris water maze without affecting acquisition or short-term memory. This suggests an effect on consolidation processes. Moreover, jHFD consumption delayed spatial reversal learning. jHFD intake did neither affect basal expression of pro-inflammatory cytokines at the periphery nor in the brain, but potentiated the enhancement of Interleukin-1-beta and Tumor Necrosis Factor-alpha expression specifically in the hippocampus after a peripheral immune challenge with lipopolysaccharide. Interestingly, whereas the same duration of HFD intake at adulthood induced similar weight gain and metabolic alterations as jHFD intake, it did neither affect spatial performance (long-term memory or reversal learning) nor lipopolysaccharide-induced cytokine expression in the hippocampus. Finally, spatial reversal learning enhanced Interleukin-1-beta in the hippocampus, but not in the frontal cortex and the hypothalamus, of jHFD-fed rats.

These results indicate that juvenile HFD intake promotes exaggerated pro-inflammatory cytokines expression in the hippocampus which is likely to contribute to spatial memory impairment.

1. Introduction

Obesity has doubled worldwide in the last thirty years, becoming pandemic (WHO, 2013). Overconsumption of energy-dense food is advanced as the major explanation for the current increase of overweight and obesity, including for children and adolescents (Ervin and Ogden, 2013). Obesity is one of the major public health challenges, since it is directly linked to various co-morbidities such as cardiovascular diseases, metabolic disorders and some cancers. In addition, studies started to demonstrate that obesity is associated with cognitive deficits in humans, especially declarative memory which depends on the hippocampus (for review, see Francis and Stevenson, 2013; Nilsson and Nilsson, 2009; Sellbom and Gunstad, 2012). In rodents, high-fat diet (HFD)-induced obesity impairs learning and memory processes, in particular those dependent on the hippocampus (for review, see Kanoski and Davidson, 2011). Obesity is increasing at an alarming rate in children and adolescents. This can be particularly problematic as these developmental periods are crucial for the maturation of the hippocampus (Spear, 2000). Using short exposure (2 months) to a HFD which exerts no effects on hippocampal function when given at adulthood

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we were able to reveal juvenile vulnerability to the effects of HFD. Indeed, exposure to this HFD from weaning to adulthood, i.e., covering adolescence, induced substantial impairment on both hippocampal plasticity and hippocampal-dependent memories indicating the juvenile period is particularly sensitive to the effect of HFD (Boitard et al., 2012).

While the mechanisms involved in the effect of HFD consumption on hippocampal-dependent memory remain poorly understood, inflammation has been proposed as a potential candidate. Indeed, there is a tight link between pro-inflammatory cytokines and hippocampal-dependent learning (for reviews: Marin and Kipnis, 2013; Yirmiya and Goshen, 2011). Whereas low hippocampal levels of pro-inflammatory cytokines can facilitate learning, high levels of cytokines, in particular interleukin-1 beta (IL-1β), specifically impairs memories relying on the hippocampal formation in adult non-obese rodents (Goshen et al., 2007; Rachal Pugh et al., 2001; Hein et al., 2010). Interestingly, obesity is considered as an inflammatory disease since both adipose tissue and gut microbiota contribute to the chronic peripheral low grade inflammation described in obese patients, as well as in rodent models (Clement et al., 2004; Cottam et al., 2004; Everard and Cani, 2013). In rodents, obesity is also associated with heightened levels of pro-inflammatory cytokines in the brain, and we and others have shown that this brain inflammation in obese animals is directly linked to the deficits of hippocampal-dependent memory (Dinel et al., 2011; Pistell et al., 2010).

However, these studies were conducted in adult or middle-aged animals. Therefore it remains to be investigated whether the higher sensitivity to the detrimental effects of juvenile HFD (jHFD) intake on hippocampal memory (Boitard et al., 2012) is associated with an exaggerated jHFD-induced hippocampal inflammation. To this end, we evaluated the effects of jHFD exposure, in comparison to adult HFD exposure, on hippocampal-dependent spatial memory and flexibility and assessed whether this could be linked to a higher cytokine production in the hippocampus. Pro-inflammatory cytokines were first measured at basal state at the periphery and in different brain structures (hippocampus, frontal cortex and hypothalamus). Then, we explored whether jHFD intake could exacerbate this cytokine production in response to a well-defined stimulatory condition, i.e., a systemic acute immune challenge. Finally, as hippocampal-dependent learning is able to increase pro-inflammatory cytokines in the hippocampus (Goshen et al., 2007; Labrousse et al., 2009), we assessed cytokine levels following our learning paradigm in control and jHFD-fed animals.

2. Materials and methods

2.1. Animals and diets

Animals were Wistar naïve male rats (Robert Janvier, Le Genest St-Isle, France) aged either 3 weeks old (juvenile groups) or 12 weeks old (adult groups) on arrival. They were housed in groups of 2–4 individuals in polycarbonate cages (48*26*21 cm) in a air-conditioned (22 ± 1 °C) animal-keeping room maintained under a 12:12 LD cycle. Animals had *ad libitum* access to food and water and were weighted once a week since arrival until sacrifice. On arrival, animals of both groups of age were divided in 2 groups with no weight differences, one receiving control diet, containing 2.5% lipids and offering 2.9 Kcal/g (CD, A04 SAFE, Augy, France) and the other receiving HFD containing 24% lipids and offering 4.7 Kcal/g (D12451, Research Diets, New Brunswick, NJ, USA). One week before the behavioral task, rats were isolated in individual cages (35*23*19 cm) and habituated to be handled by the experimenter. Rats were exposed to CD or HFD for 2 or 3 months starting either at weaning (3 weeks-old; jCD and jHFD groups), i.e., throughout adolescent development (from weaning to adulthood; Spear, 2000), or at adulthood (starting at 12 weeks-old; aCD and aHFD groups) before the beginning of behavioral tasks (Fig. 1). Some animals were exposed to CD or HFD for only one month starting at weaning in order to cover adolescence in a more restrictive manner (Fig. 1). All behavioral experiments were performed on adult animals still consuming their respective diet at the time of testing and sacrifice occurred after 4 months of diet exposure (Fig. 1).

2.2. Behavioral task: the spatial version of the Morris water maze (MWM)

2.2.1. Apparatus

A circular tank (150 cm in diameter and 50 cm high) was filled with water (22 ± 2 °C) made opaque by addition of white paint. A platform (10 cm diameter, 30 cm away from the edge of the tank) was submerged 5 cm underneath the water surface, therefore not visible for the rats. Visual cues are provided on the walls of the room to allow spatial navigation. A camera wired to an automated tracking system (SMART v2.5.20, Panlab, Barcelone, Espagne) allows recording the rat's pathway and behavior.

2.2.2. Learning schedule

During 5 consecutive days, rats were trained to localize the platform. Rats underwent 6 trials per day, with different starting locations for each trial, following a pseudo-random sequence. Before the very first trial, rats were placed on the submerged platform during 30 s. Then every trial consisted in a swim, followed by a 30 s rest on the platform. Rats that did not reach the platform within 90 s were guided to it by the experimenter. The inter trail interval was of 15 s. Latency to reach the platform, distance travelled and swimming speed were recorded.

2.2.3. Classical memory assessment

Memory was assessed through probe tests occurring 2 h (short-term memory assessment) and 4 days (long-term memory assessment) after the last learning session unless stated otherwise. The platform was removed and rats were allowed to navigate in the water maze during 90 s.

Latency to reach to target annulus, time spent in the quadrants (each representing ¼ of the maze) and the number of each annulus crossings (one in each quadrant, the target annulus being the one where the platform was localized during learning) were recorded (used as the classical measures of water maze test performance: see Maei et al., 2009). Only the annulus crossings were analyzed and presented here for two reasons. First, the number of annulus crossings reveals a more accurate search of the platform than the time spent in the quadrants (see Florian et al., 2006; Serrano et al., 2008). Second, if all variables show that CD-fed rats are able to locate the platform during the first probe trial, only annulus crossings are relevant for this control group during subsequent probe trials (above chance level).

2.2.4. Memory updating

In order to assess spatial memory updating, known to be hippocampal-dependent (Rossato et al., 2006), other animals were trained in the same learning protocol as described above after juvenile or adult diet exposure (Fig. 1). The day after learning, rats were submitted to a reversal learning protocol. The reversal learning consisted of only one session of 6 trials, with the platform in the opposite location than during the initial learning. A probe test was performed 24 h after reversal learning. However, since none of the groups exhibited preference for target quadrant or annulus during this probe test, data of this probe trial is not shown.