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Chronic high fat diet consumption impairs sensorimotor gating in mice

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Summary Chronic intake of high fat diets (HFD) has been long recognized to induce neuronal adaptations and impair elementary cognitive functions. Yet, the consequences of chronic HFD consumption on central information processing remain elusive. The present study thus explored the impact of chronic HFD consumption on pre-attentive central information processing using the paradigm of prepulse inhibition (PPI) of the acoustic startle reflex in mice. Animals were fed an experimental diet with 60% of its calories derived from fat, and were compared to control low fat diet (LFD, 10% calories from fat) fed animals. A first experimental series demonstrated that adult mice exposed to chronic HFD throughout adolescent development displayed significant deficits in PPI compared to LFD-fed mice. Identical chronic HFD treatment further led to presynaptic dopaminergic abnormalities in the form of increased tyrosine hydroxylase density in the nucleus accumbens core and shell subregions. Moreover, we found that tyrosine hydroxylase density in the nucleus accumbens shell negatively correlated with the mean PPI scores, suggesting a potential contribution of the accumbal dopamine system to HFD-induced PPI deficits. This impression was further supported by an additional series of experiments showing that the HFD-induced attenuation of PPI can be mitigated by systemic administration of the dopamine receptor antagonist haloperidol. Finally, HFD feeding was sufficient to disrupt PPI when its exposure was restricted to the peripubertal period, whilst the same manipulation failed to affect PPI when limited to adulthood. In conclusion, our findings emphasize that pre-attentive information processing as assessed by the PPI paradigm is highly sensitive to nutritional factors in the form of chronic HFD consumption, especially when initiated during peripubertal maturation. It is likely that the disrupting effects of HFD on sensorimotor gating involve, at least in part, dopaminergic mechanisms.

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1. Introduction

Chronic intake of high fat diets (HFD) is strongly associated with the development of a number of metabolic disturbances, including obesity, type-2 diabetes, and cardiovascular disease (Hu et al., 2001). Converging evidence from experimental work in animals and clinical investigations in humans indicates that excessive consumption of such "Western diets" can also lead to neuronal adaptations and impair elementary cognitive functions (Francis and Stevenson, 2013). Dietary effects on the hippocampus and prefrontal cortex have received wide appreciation in this context because cognitive performance critically depends on the integrity of these brain areas (Kanoski et al., 2007; Kanoski and Davidson, 2011). Owing to its negative impact on brain functions, chronic HFD intake has also been associated with an elevated risk of neurological disorders that are characterized by (progressive) cognitive impairments, most notably Alzheimer's Disease (AD) and other forms of dementias in aging (Hildreth et al., 2012).

In the present study, we set out to explore the impact of chronic HFD consumption on pre-attentive central information processing using the paradigm of prepulse inhibition (PPI) of the acoustic startle reflex. PPI refers to the reduction of the startle reaction to a startle-eliciting stimulus (pulse) when it is shortly preceded by a weak stimulus (prepulse) (Hoffman and Searle, 1965; Graham, 1975). PPI is an operational measure of sensorimotor gating, in which central gating mechanisms protect the processing of the information contained in the initial prepulse from distraction by the subsequent pulse stimulus (Swerdlow et al., 2000). PPI thus reflects the ability to filter or gate intrusive sensory-motor information, and this phenomenon can be readily demonstrated in a variety of species, including humans and rodents (Swerdlow et al., 1999).

A direct association between excessive intake of dietary fat and abnormalities in sensorimotor gating has thus far not been established. However, this possibility seems likely given some findings linking metabolic disturbances to PPI attenuation. First, significant PPI deficits have been reported in *db/db* mice, which harbor an autosomal recessive point mutation in the leptin receptor gene and are characterized by multiple metabolic dysfunctions, including hyperphagia, progressive hyperglycemia, and obesity (Sharma et al., 2010). Second, an indirect link between hyperphagia, excess fat deposition, and emergence of PPI deficits has also been established in an inflammation-mediated developmental pathogenesis model in mice (Pacheco-López et al., 2013). Deficits in PPI are also commonly (but not exclusively) observed in patients with schizophrenia (Braff et al., 2001), a chronic mental illness characterized by widespread psychopathological symptoms. Schizophrenic patients often display metabolic disturbances even prior to the initiation of chronic antipsychotic medication (Thakore et al., 2002; Verma et al., 2009; Kirkpatrick et al., 2012) and are frequently reported to consume saturated fat diets more excessively than healthy controls (reviewed in Dipasquale et al., 2013). Yet, the extent to which excessive HFD intake in this clinical population may actually contribute to the emergence of psychopathological symptoms such as PPI deficiency remains elusive.

These considerations prompted us to seek evidence for a possible causal relationship between chronic HFD consumption and sensorimotor gating dysfunctions in mice. To mimic chronic HFD intake, animals were fed an experimental diet with 60% of its calories derived from fat, whereas control low fat diet (LFD) animals were fed a diet with only 10% of its calories from fat. First, we compared the effects of chronic HFD or LFD feeding given throughout adolescent development on PPI in adulthood. In animal models, cognitive effects of chronic HFD exposure have mostly been studied following a dietary intervention restricted to adulthood (Winocur and Greenwood, 2005). Recent findings suggest that chronic HFD exposure during peripubertal development may exert a more extensive negative impact on cognitive functions compared to identical dietary exposure in adulthood (Boitard et al.,

Table 1 Summary of the different experimental series. Animals in cohort 1 were exposed to chronic low fat diet (LFD) or high fat diet (HFD) for 8 weeks throughout adolescent development, that is, from postnatal days (PND) 28 to 84. Behavioral testing was conducted on PND 84 before they were sacrificed for the purpose of post-mortem immunohistochemical analyses 1 week later on PND 91 (not shown in table). Animals in cohort 2 were also exposed to LFD or HFD throughout adolescent development for 8 weeks from PND 28 to 84. These animals were pre-treated with the dopamine receptor antagonist haloperidol (HAL) or vehicle (VEH) before prepulse inhibition testing. Animals in cohort 3 were exposed to HFD or LFD for 4 weeks either between PND 28 and 56 (puberty), or between PND 70 and 98 (adulthood exposure). Prepulse inhibition testing was conducted on the last day of the pubertal or adult dietary intervention (i.e., on PND 56 or 98).

Cohort	Experimental series	Age when diet was given	Number of weeks on diet	Experimental groups	Group Size
1	Chronic exposure throughout adolescence	PND 28–84	8	LFD	10
				HFD	10
2	Influence of haloperidol after chronic exposure throughout adolescence	PND 28–84	8	LFD/VEH	8
				LFD/HAL	9
				HFD/VEH	8
				HFD/HAL	9
3	Influence of developmental timing of dietary exposure	PND 28–56	4	LFD/Puberty	12
				HFD/Puberty	12
		PND 70–98	4	LFD/Adulthood	12
				HFD/Adulthood	12