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Fatty acid amide supplementation decreases impulsivity in young adult heavy drinkers

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HIGHLIGHTS

- False alarm rate on Go/No-Go has been linked to dorsal striatal dopamine adaptation.
- OEA supplementation does not change self-reported impulsivity (BIS-11).
- OEA supplementation reduces false alarms on a Go/No-Go task in heavy drinkers.
- Improved sensitivity on a Go/No-Go task is associated with reduced alcohol intake.

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ABSTRACT

Compromised dopamine signaling in the striatum has been associated with the expression of impulsive behaviors in addiction, obesity and alcoholism. In rodents, intragastric infusion of the fatty acid amide oleoylethanolamide increases striatal extracellular dopamine levels via vagal afferent signaling. Here we tested whether supplementation with PhosphoLean™, a dietary supplement that contains the precursor of the fatty acid amide oleoylethanolamide (N-oleyl-phosphatidylethanolamine), would reduce impulsive responding and alcohol use in heavy drinking young adults. Twenty-two individuals were assigned to a three-week supplementation regimen with PhosphoLean™ or placebo. Impulsivity was assessed with self-report questionnaires and behavioral tasks pre- and post-supplementation. Although self-report measures of impulsivity did not change, supplementation with PhosphoLean™, but not placebo, significantly reduced false alarm rate on a Go/No-Go task. In addition, an association was found between improved sensitivity on the Go/No-Go task and reduced alcohol intake. These findings provide preliminary evidence that promoting fatty acid derived gut-brain dopamine communication may have therapeutic potential for reducing impulsivity in heavy drinkers.

1. Introduction

Deficient dopamine signaling has been implicated as both a cause and a consequence of obesity, alcoholism and addiction [1,2]. With respect to obesity, in rodent models a high fat diet increases adiposity, decreases extracellular striatal dopamine response to nutrients [3], decreases D2 receptor density in the striatum and increases compulsive responding for food [4]. Neuroimaging studies suggest parallel effects in humans. Overweight/obese compared to healthy weight individuals show reduced change in striatal D2 receptor binding potential in response to glucose ingestion (consistent with reduced dopamine release) [5] and several studies have reported a negative association between body mass index (BMI) and the blood oxygen level dependent (BOLD) response to milkshake consumption in the caudate nucleus [6–8]. Although BOLD does not directly measure dopamine release, this effect is dependent upon the TaqIa A1 polymorphism, which affects D2 receptor density, thus linking the BOLD response to D2 receptor signaling [6]. Consistent with the rodent work, the decreased response also appears to be a consequence rather than a cause of obesity since it is associated with weight gain [9], but not risk for obesity [10]. Finally, and critical for the aim of the current study, lower BOLD response to milkshake in the caudate nucleus is associated with increased impulsivity, especially in overweight/obese individuals [8]. Collectively these findings suggest that a diet high in fat and/or increased adiposity results in dopamine adaptions in the dorsal striatum that increase impulsive behaviors, which are themselves a risk-factor for obesity [11].

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Table 1
Subject anthropometric & demographic data of two groups based on intake measures.[a]

	PhosphoLean (n = 11)	Placebo (n = 11)	p-Value
Age (years)	27.3 ± 7.89	25.3 ± 4.35	0.47
Male sex (n,%)	7 (63.6%)	6 (54.5%)	0.68
BMI (kg/m^2)	25.7 ± 4.99	24.7 ± 3.69	0.62
Education (years)	15.8 ± 1.83	15 ± 2.1	0.34
BDI	4.8 ± 4.21	2.7 ± 2.76	0.18
BAI	3.4 ± 4.37	2.5 ± 3.64	0.60
NAART	19.2 ± 6.84	18.5 ± 9.09	0.85
TONI	41.2 ± 8.93	41 ± 8.28	0.96
Smoking (cig.)	0.6 ± 1.57	1.4 ± 3.59	0.54
Alcoholic drinks (avg. p.w.)	14.9 ± 11.77	16.4 ± 8.97	0.74
THC	0.3 ± 0.48	0.4 ± 0.5	0.77

[a] Values are expressed as mean ± standard deviation or n (%).

The exact mechanism by which this effect occurs in humans is unknown. However, recent work in the animal model suggests that compromised fatty-acid derived brain-gut communication plays a role. Nutrient infusion directly into the gut increases extracellular dopamine levels [3]. This response is compromised following a high fat diet, which concomitantly depletes intestinal levels of N-Acylethanolamines, a family of appetite-regulating fatty acid amides [12,13]. One such amide [14], oleoylethanolamide (OEA), which is synthesized in the intestine in response to dietary oleic acid [15], not only acts as a powerful satiety messenger by signaling via a nuclear receptor peroxisome proliferator-activated receptor alpha (PPARα) [16], but also reverses diet-induced blunted striatal dopamine signaling [3]. Specifically, placing mice on a high fat diet decreases OEA levels in the intestine and blunts the rise in extracellular striatal dopamine normally observed in response to intragastric infusion of lipids. This blunting may then be reversed by intraperitoneal infusion of OEA. OEA infusion can also potentiate dopamine release in response to a low-fat intragastric infusion in lean animals on a low fat diet, an effect accompanied by a decrease in preference for high fatty foods demonstrating that the ability of OEA to influence striatal dopamine efflux is not restricted to the context of diet-induced dopamine adaptations [3]. Furthermore, intragastric injection of OEA in lean mice causes a decrease in preference for high fatty foods [17]. Whether similar effects can be observed in humans is unknown; however, plasma OEA levels are associated with brain responses to food images [18] and supplementation with the dietary supplement PhosphoLean™, which contains N-oleyl-phosphatidyl-ethanolamine (NOPE), the precursor for OEA, increases compliance with weight loss programs [19,20], possibly indicating a beneficial effect of supplementation on self-control.

Similar to a high fat diet, prolonged heavy drinking of alcohol is associated with altered dopamine signaling [21] and impulsivity [11]. Alcohol abuse also clearly alters lipid metabolism [22] and liver function [23]. Similar to the effect of a high fat diet on OEA, alcohol intake releases OEA, and chronic ethanol administration decreased OEA levels in parallel with the onset of withdrawal symptoms [24]. Even more critically, OEA administration can block cue-induced reinstatement of alcohol-seeking behavior (the animal model for relapse). This suggests the intriguing possibility that OEA may be a novel therapeutic target for alcohol use disorders and alcoholism. With this in mind we set out to perform a preliminary study to test if dietary supplementation with a fatty acid amide could reduce alcohol intake and impulsivity in a group of young adult heavy drinkers. Twenty-two participants underwent three weeks of dietary supplementation with PhosphoLean™ (30 mg N-oleyl-phosphatidyl-ethanolamine (NOPE) + 20 mg epigallocatechin-3-gallate (EGCG) per capsule) or treatment with placebo. We predicted that impulsivity would decrease in the PhosphoLean™, but not placebo group, and that decreases in impulsivity would be associated with reduced alcohol intake. Given the animal data linking OEA administration with change in preference for fat [17] and to consider potential effects of OEA food choice, we also measured fat concentration preference.

2. Materials and methods

2.1. Participants

Twenty-two healthy human adults ranging in age from 21–45 years participated in the study. Participants had to meet NIAAA heavy drinking criteria [25] (5 or more standard drinks for men and 4 or more standard drinks for women on a drinking day) at least once per week for the prior 21 days, but they had to consume less than 40 drinks in total per week. Further criteria include right handedness, English speaking, and a body mass index (BMI expressed as kg/m^2) within the range 18.5–35.

Participants were excluded if they had a past or current history of alcohol or drug abuse or dependence, or tested positive on any toxicology tests performed at each session (reported past or current use or positive test for Tetra Hydro Cannabinol (THC) was allowed), medical illness, psychiatric illness as defined by the DSM-IV criteria including eating disorders, medications that affect alertness, history of head trauma with loss of consciousness, diabetes, food allergy or ongoing pregnancy. Out of 29 recruited subjects seven did not complete the study: four because they were ineligible, two due to scheduling issues and one for not wanting to take the supplement.

Participants were recruited with flyers and online advertisements in the Yale University and the greater New Haven communities. Written informed consent was obtained and the protocol was approved by the Yale University Human Investigations Committee.

2.2. Supplement

PhosphoLean™ is a dietary supplement consisting of N-oleyl-phosphatidyl-ethanolamine (NOPE) and epigallocatechin-3-gallate (EGCG). NOPE is extracted from soy phospholipids and EGCG is from standardized green tea extract. NOPE consists of OEA bound to phosphatidylethanolamine (PE). NOPE is a naturally occurring ethanolamine glycerol-phospholipid containing three fatty acid chains and is found in animal and vegetable foods that are part of the human diet. OEA activates PPARα found in the intestine tract through binding after oral admission [16]. EGCG polyphenols act synergistically with OEA via sympathetic activation of thermogenesis and increases fat oxidation [26]. Every capsule, supplied by CHEMI Nutra (White Bear Lake, MN),

Table 2
Data and statistics of anthropometrics.

	PhosphoLean (n = 11)[a]		Placebo (n = 9)[a]		Time × group interaction		Pairwise comparison p	
	Pre-test	Post-test	Pre-test	Post-test	F	p	PhosphoLean	Placebo
Multivariate	–	–	–	–	[3,15][b] 1.388	.285	–	–
Univariate								
BMI (kg/m^2)	26.2 ± 5.91	26.14 ± 5.69	25.58 ± 5.22	26.09 ± 5.45	[1,17] 2.489	.133	.618	.113
BF (%)	28.19 ± 12.62	26.86 ± 12.63	24.9 ± 11.76	24.15 ± 12.09	1.154	.298	.125	.994
W/H ratio	0.91 ± 0.05	0.88 ± 0.08	0.88 ± 0.07	0.86 ± 0.09	1.444	.246	**.040**	.700

Bold font indicates statistically significant P-values of P < 0.05 and trends of P < 0.1.
[a] Values are expressed as mean ± standard deviation or n (%).
[b] Degrees of freedom [hypothesis, error].