

## Application Example: Quantitation of a Chemical Messenger Linking the Gut to Brain Reward Centers

### Summary

Why do children prefer to eat cookies rather than carrots? The reason may be that high-fat foods activate a reward circuit in the brain that results in the release of dopamine, a neurotransmitter that regulates pleasure. Every type of reward that has been studied, from high fat foods to sex to addictive drugs such as cocaine act by increasing dopamine in reward centers in the brain. Overeating high-fat foods may dampen this dopamine-signaling reward sensation and set in motion an “obesity cycle” that provokes progressively more eating of even more high-fat foods in an effort to achieve the same level of reward. The mechanisms by which dietary fat in the gut signals the brain to release dopamine are unclear. Tellez *et al* (2013) suggest that a chemical messenger, oleoylethanolamine (OEA), that is synthesized in the intestines may be the “missing link”. Mice on a high-fat diet had unusually low levels of intestinal OEA and a reduced dopaminergic response to gut stimulation with high-fat lipids. Intraperitoneal or intestinal infusion of OEA restored the dopaminergic response to normal levels and mice that had been accustomed to a high-fat diet began to eat more low-fat foods. Restoring gut-generated lipid signaling may increase the reward value of less palatable, healthier foods. Intriguingly, research is underway to determine if the OEA signaling pathway may restore normal brain responses to food in obese humans.

In recognition of the importance of this work, the Tellez *et al* (2013) publication has been recommended for inclusion in the F1000Prime directory of top articles in biology and medicine. The F1000Prime recommendation, which can be viewed here: <http://f1000.com/prime/718078456?subscriptioncode=b613440fac16-47c0-9638-2d8b770c5244> mentions that, “The clinical and conceptual implications of the study are

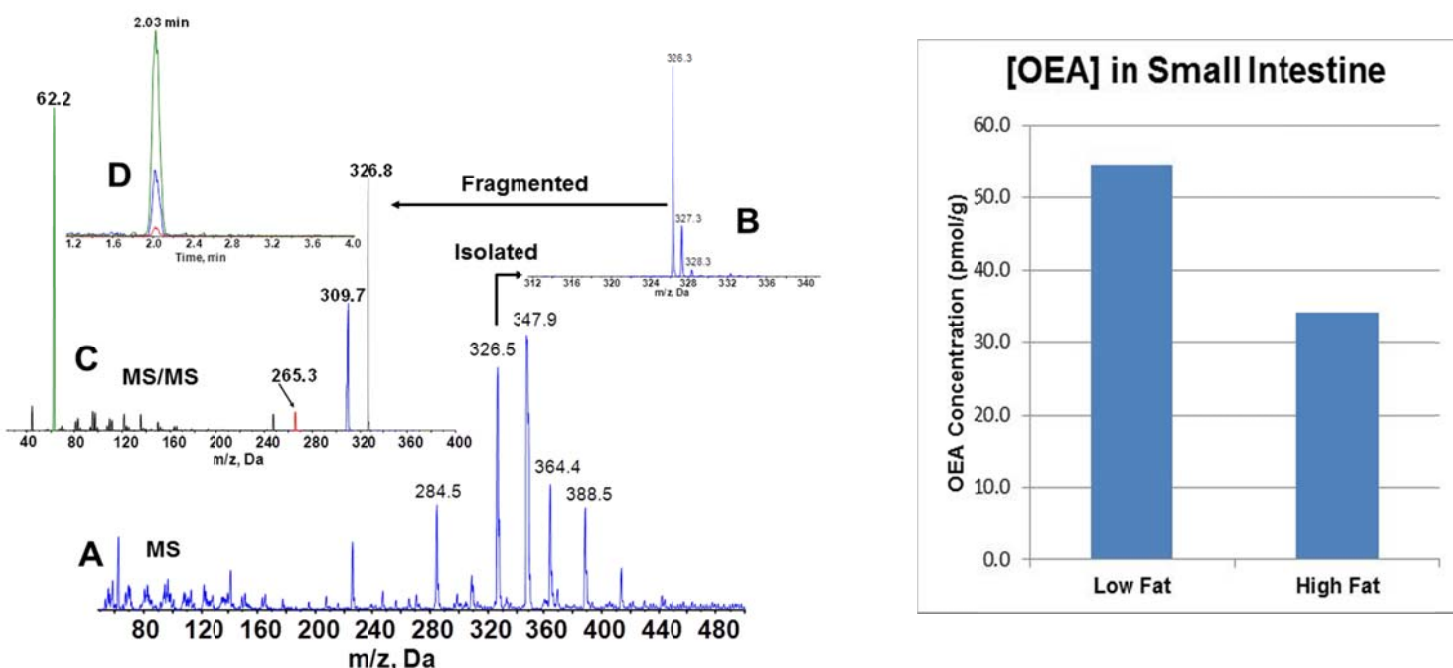


Fig.1: OEA Lipid Quantitation by LC-MRM on a 4000 Q-TRAP

profound, but perhaps most striking is the strength of the connection between the gut and key brain centers that influence complex behavior.”

### **Methodology**

Low fat (LF, N=8) and high fat (HF, N=8) fed mice were euthanized and lipids extracted from the small intestine. The lipid extracts were analyzed using an LC-MRM assay on a Perkin Elmer UPLC System coupled in-line to a 4000 Q-TRAP mass spectrometer. The left side of Figure 1 shows the development of the LC-MRM assay with (A) showing the broadband mass spectrum of the OEA standard with OEA at m/z 326.8. The OEA parent ion is mass selected in Q1 (B), fragmented in Q2 (C), and product ions (transitions) at m/z 62.2, 265.3, and 309.7 are selected and detected in Q3 (D). All three product ions (color coded in C) were monitored and, as expected, have similar retention times (shown in D). OEA was quantified based on the average intensities of these three transitions relative to an internal, deuterated OEA standard. The right side of Figure 1 shows that HF mice synthesized significantly less OEA in small intestine compared to LF mice ( $34.0 \pm 4.6$  vs.  $54.5 \pm 4.3$  pmol/g of tissue respectively; Two-sample t-test  $t_{14}=3.2$ ,  $p=0.0061$ ).

### **Literature Cited**

Tellez, L.A., Medina, S., Han, W., Ferreira, J.G., Licon-Limon, P., Ren, X., Lam, T.T., Schwartz, G.J., and de Araujo, I.E. (2013) A gut lipid messenger links excess dietary fat to dopamine deficiency, *Science* 34, 800-802.