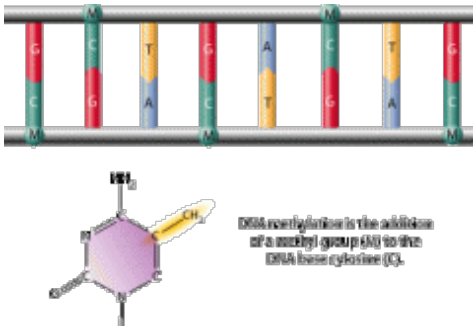
Five Methylations that are Making Your Kids Overweight

By Amielle Moreno

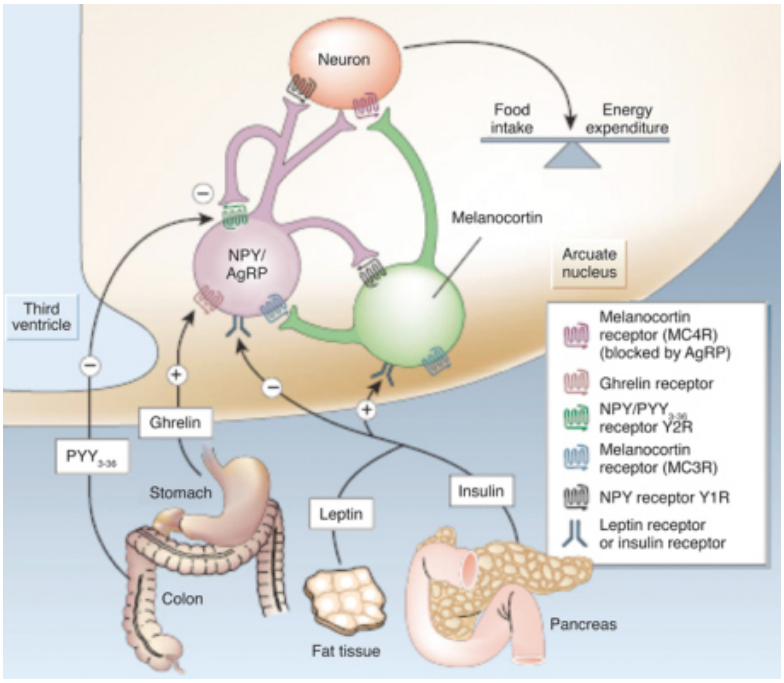
Eating behavior is a choice, yet we often forget that urges to eat are regulated not just by the discomfort of an empty stomach, but by a complex feeding systems that induce hunger and satiety. A combination of logic and impulse is involved every time we put calories in our mouths and the lasting changes these calories enact in our bodies, and specifically our DNA, is only now being discovered.



By adding a methyl group (-CH3) to a section of DNA it becomes more difficult for transcription machinery to read it. In this way the expression of genes can be controlled by DNA methylation. This is called 'epigenetics.' Research suggests that these modifications can be passed on to the next generation.

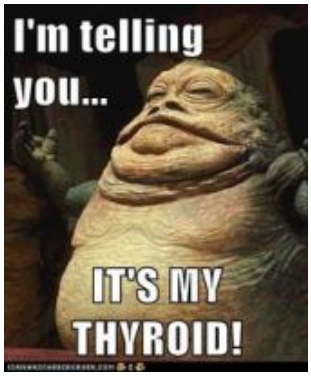
In a recent issue of Cell, first author Ida Donkin examined the sperm of human men, to determine if these epigenetic modifications are altered by feeding behavior. In her scientific paper *Obesity and Bariatric Surgery Drive Epigenetic Variations of Spermatozoa in Humans*, mass-sequencing results identified the location of DNA methylation modifications in the genome of lean, obese, pre-bariatric (think stomach bypass) and post-bariatric surgery men's sperm.

Among many genes associated with anatomical structure and cell fate, neuro-proteins were also differentially methylated between the experimental groups, indicating that not only does eating behavior enact epigenetic modifications, but also that methylation patterns are passed from father to offspring. Here are the top six neuro-proteins Donkin's found destined to be expressed differently between overweight and lean men.



Take that, New Year's resolution! (Lizarbe, 2013)

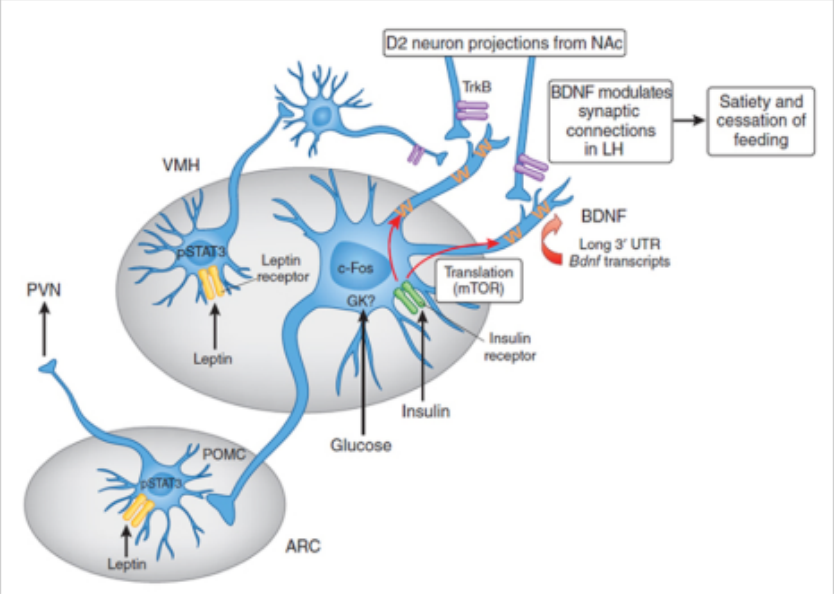
Melanocortin-4 Receptor (MC4R): Compared to Hypothyroidism or Cushing's syndrome, MC4R is a less commonly known inherited cause of childhood and adult obesity. Genome-wide studies of body mass index (BMI) confirmed the link between obesity and having DNA variants downstream of the MC4R gene (Loos, 2008). Highly expressed in the hypothalamus, MC4R plays an essential role in energy balance (Siljee, 2013).



Hererozygous mutations are responsible for uncontrolled release of growth hormones, causing increased height and weight starting in childhood (2.5 to 6% of all cases) and continuing into adulthood (5.8% of adult obesity cases; Siljee, 2013; Farooqi, 2003). This receptor is responsible for homeostatic signals indicating that fat is being ingested (Butler, 2001). By letting the body "sense" the intake of dietary fat, activation of this receptor regulates both the metabolic and behavioral response to food, by curbing hyperphagia (overeating).

With high methylation patterns, Obese men's sperm in the study were less likely to allow receptor expression, potentially making it more difficult to "sense" food intake. Clinical trials using compounds, which activate MC4R, are currently being performed in the hopes of finding an appetite curbing treatment with few side-effects.

Brain-Derived Neurotrophic Factor (BDNF): Thought to be involved with everything from Schizophrenia to drug addiction, BDNF has its hands on everything. The *Bdnf* gene's expression increases neuron growth and it linked to long-term potentiation and long-term memory. Physical exercise has been shown to increase the synthesis of BDNF in the human brain, improving cognitive function, neurogenesis and mood (Szuhany, 2015). Donkin's has found evidence that simply by decreasing weight via surgery, the methylation of a gene associated with cognition can change. Thus "GBP-induced weight loss modulates the epigenetic landscape of spermatozoa and alters specific genomic regions" in genes associated with cognition.



Just a collection of letters and shapes (Schwartz, 2012).

Neuropeptide Y (NPY): This protein provides you everything you ever wanted in life: reduced anxiety and stress, reduced pain perception, lower blood pressure… except for the part about increasing fat storage, and carbohydrate appetite (Stanley, 1986). To aid in homeostasis, our adipose tissues produce peptide hormones. These signals are sensed by receptors, such as MC4R, in the hypothalamus brain region to regulate appetite.

This research has prompted Cinnabon to expand into the standardized testing business.

Peptides, such as leptin and insulin, shut down the release of NPY to curb hyperphagia. There is a strong link between stress and this potent appetite enhancer because the glucocoritcoid hormones produced during stress leads to an increase in NPY release (Arora, 2006). More like a dimmer than an on-off light switch, the amount of NPY released during stress is correlated to the level of stress experienced (Kuixing, 2012).

Cannabinoid receptor type 1 (CR1): Cannabinoid receptors are the most highly expressed G-protein receptors in the brain (Glass, 1997). Unfortunately, studies are limited by the fact that CR1 has different expression patterns in mice compared to humans. Receptor activation in mice mostly leads to them running around more, because of the heavy cerebellum expression, leaving scientists with no good model organisms for experimentation.

In humans, CR1 is expressed in so many different areas of the human brain that listing them wouldn't help explain its actions. But perhaps its expression in the areas of the brain involved with processing reward, such as the basal ganglia and substantia nigra, could explain its connection to feeding behavior. Any Washingtonian or Coloradan knows that ingesting the exogenous THC molecule will induce feeding behavior, because of its interaction with the CR1 receptor (Williams, 1999). Even though its activation is not essential for feeding behavior, blocking CR1 would lead to better control of appetite. However, few clinical trials have assessed intervention that up regulates the CB system, presenting a need to explore it as a promising intervention (Williams, 2014).

If only academic scientists had a population of potential test subjects willing to experiment with drugs

Cocaine and Amphetamine related transcript (CART): CART is a neuropeptide that produces similar behavior in animals to cocaine and amphetamine, such as increased locomotor and a preference for places associated with the drug (Nakhate, 2011). CART peptide's expression is regulated by leptin and ghrelin and interacts with several hypothalamic appetite circuits. Researchers have targeted this peptide as a possible treatment for eating disorders, cocaine abuse and even Parkinson's disease, yet its receptor is still unknown.

Donkin's study reports the methylation of a number of "*distal intergenic*" areas. Located between genes, *distal intergenic* is another way of saying *junk DNA* which, is another way of saying *we don't know what it does yet*. The CART and NPY genes show *higher* levels of methylation in the sperm of Lean versus Obese men at specific distal intergenic areas. This finding suggests that these locations are not junk DNA but are involved with increasing CART gene expression, making them prime targets for future experimental research.

Behind cravings and overeating there's a complex neurological system ready to be blamed. Donkin's paper provides evidence that simply reducing intake (post-GBP surgery group) can affect the expression of 2681 genes, which are differently expressed between Obese and Lean men. Although this new article still doesn't answer the pressing question of "how" spermatozoa production factors in recent behavior or environmental changes, it indicates the existence of an epigenetic mechanism, which could effect behavior across generations. Perhaps the most important takeaway is that methylation can change to aid in more healthy homeostatic regulation benefiting the individual and their offspring.

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