The role of BDNF in energy metabolism

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Abstract

Obesity is rapidly becoming a great problem for western societies. A possible target for treatment may be found in the BDNF system. BDNF affects energy balance by altering both energy intake and energy expenditure. Energy intake is decreased by hypothalamic BDNF administration, by diminishing food intake through hypothalamic mechanisms. The craving for high fat meals is also diminished by acting on the dopaminergic system. In addition, energy expenditure is elevated following hypothalamic BDNF administration or overexpression, partly by increasing locomotion, and partly by increasing the RMR by increasing thermogenesis. Locomotion may be affected by BDNF via an increase of CRH expression, while alteration of thermogenesis may be due to affecting sympathetic nervous system output in BAT. A phenotypic switch of WAT to BAT has been linked to BDNF, but underlying mechanisms are unclear. Most of these effects are mediated via CRH, and glucocorticoid receptors inhibit the release of CRH by BDNF. This review theorizes GRs offer a braking mechanism on BDNFs action.

Introduction

Obesity is a growing problem in today's society. In the U.S. in 2009/2010, over 35% of adults are obese, according to an investigation by the CDC *(Ogden 2012)*. Obesity greatly increases the risk of getting heart disease, stroke, type 2 diabetes, and certain types of cancer. The leading cause of all this is an overconsumption of a western type diet and a sedentary lifestyle. An increased food intake without the proper energy expenditure pattern will lead to the storage of excess energy in adipose tissue, in muscle and several organs including the liver. Energy intake is determined by the diet and its composition, while energy expenditure is based on physical activity and the resting metabolic rate (RMR). The RMR is the amount of energy needed in a resting state at a neutral temperature, determined by thermogenesis and composition of the body.

A possible regulator for energy metabolism is Brain-Derived-Neurotrophic-Factor (BDNF). BDNF is a protein found in many areas of the body, and it acts on the TrkB receptor. This receptor is expressed in certain areas of the brain, including the hippocampus and hypothalamus. It has been linked to learning and memory functions *(Yamada 2003)* and stimulates neuronal growth and differentiation whilst protecting existing neurons. Conistent with this idea is a recent case report of a girl who had been diagnosed with hyperphagia, obesity, decreased cognitive function and hyperactivity *(Gray 2006)*, resulting from a de novo chromosomal inversion in a region encompassing the BDNF gene. Her serum levels of BDNF were reduced with age- and BMI-matched controls *(Gray 2006)*. BDNF is a member of the nerve growth factor (NGF) family, and the TrkB receptor is of the tyrosine kinase type. This receptor is highly expressed in brain regions associated with energy metabolism like the hypothalamus *(Yan 1997)*. Studies in rodent models have shown that BDNF regulates energy balance by increasing energy expenditure, whilst reducing food intake *(Kernie 2000, Tsuchida 2001, Wang 2007, Naert 2006)*. However, the circulating levels of BDNF vary between individuals, which in part may be due to differences in diet composition. An unhealthy, high fat diet has been shown to be associated with a reduced amount of circulating BDNF in humans *(Karczewska-Kupczewska 2011)*. Also, FFA's levels are elevated in obese individuals because the enlarged adipose tissue mass releases more FFA, and higher levels of FFA will inhibit insulin's anti-lipolytic action, further increasing the amount of FFA released *(Carnell, 2008, Boden 2008)*. If BDNF is linked to regulating energy balance and is reduced in obese individuals, it may seem a good target to help these obese individuals lose weight.

This review will focus on the various ways BDNF influences energy balance. What effect does BDNF have on the aspects of metabolism? Which underlying pathways or mechanisms can explain these effects? And finally, does BDNF offer a possible treatment for obesity in humans?

Locomotion

Locomotion, or spontaneous physical activity (SPA), is an important aspect of energy expenditure, and thus of energy balance. A sedentary lifestyle obviously greatly reduces energy expenditure, and this is a great risk factor of attracting obesity. Indeed, obese individuals usually show less activity than their lean counterparts (*Levine 2001)*. The neurobiological underpinnings of SPA have been investigated in animal models, mostly mice and rats *(Garland 2011)*. Some studies mention a dissociation between horizontal and vertical activity, but do not explain what the differences exactly mean. Vertical activity is the upright behavior of an animal, when it is standing on its hind legs exploring the surroundings. Horizontal activity may be more relevant when making a comparison with humans, as this is locomotion. Still, active humans not only show more locomotion, but show more behavioral activity unrelated to locomotion, like fidgeting, changing body posture, position etc. (Levine 2001).

The effect on BDNF on this subject is contradictory. Some studies suggest that BDNF increases SPA. Specifically, continuous infusion of BDNF in the lateral ventricle of mice with an osmotic pump increased SPA significantly in the long term *(Naert 2006)*. Heterozygous BDNF null mice display less horizontal motor activity with a reduced expression of BDNF protein in striatal tissue *(Boger 2011)* and bilateral tissue punches of cortex, striatum, hippocampus, and ventral mesencephalon–diencephalon *(Saylor 2006)*. However, there are also studies showing the opposite. For example, the girl with the chromosomal inversion mentioned in the introduction shows hyperactivity with reduced BDNF levels *(Gray 2006)*. Studies using a different strain of heterozygous BDNF null mice show an increase of SPA in BDNF deficient mice too *(Kernie 2000, Rios 2001, Dluzen 2000)*, implying that BDNF decreases activity. One of these studies showed a deficiency of BDNF in the hypothalamus, hippocampus, and cortex *(Rios 2001)*, but they do not note BDNF levels in specific areas of the hypothalamus. The other two studies do not check BDNF expression levels at all. It may be so that these mice are deficient in BDNF in different areas of the brain.

Part of these varying results might be explained by the area where BDNF is acting and/or where BDNF deficiency/(over)secretion is most pronounced. Infusing BDNF in the VMH leading to an increase of locomotion *(Wang 2010)* is rather site-specific as BDNF infusion in the adjacent PVN has no effect *(Wang 2007)*. Traditionally, the VMH is known as an important regulator of SPA *(Bannai 1998, Narita 1994, Narita 2002, Zhao 2004)*. Specific deletions of steroidogenic factor-1 (SF-1) reduces endogenous BDNF levels in the VMH, resulting in a significantly decreased SPA level *(Tran 2003)*. SF-1 is known to regulate the expression of genes that are important for steroidogenesis. Other pathways may include the melanocortin system, as MC4 mutant mice have low BDNF levels in the VMH too *(Xu 2003)*. Continuous infusion in the lateral ventricle of BDNF may affect SPA at the level of the VMH directly, but may include other areas as well *(Naert 2006)*. The differences between the various strains of heterozygous mice can possibly be caused by differences between independently constructed BDNF heterozygous mouse strains. Different heterozygote strain might show normal BDNF levels in one area of the brain, and a deficiency in the other.

Subcutaneously injected BDNF also increased SPA *(Tsuchida 2001)*, which is of interest in light of the potential therapeutic effects of BDNF to treat obesity. Apparently BDNF is able to cross the blood brain barrier and influence SPA. The required dose to see an effect is

obviously a lot higher; 20 mg/kg of subcutaneous BDNF was needed. In comparison Wang et al. reported that using 0,5 µg of BDNF was sufficient when injected directly in the area of the VMH.

Effects of BDNF on SPA analogous to those with BDNF have been found with corticotropin-releasing hormone (CRH). CRH is commonly known to increase behavioral arousal, increase the activity of the sympatho-adrenal system, and mediate the hypothalamic pituitary (HPA) axis in response to stress. TrkB receptors are present on CRH synthesizing cells in the PVN *(Levin 2007, Rosas-Vargas 2011)*. Recently it has been shown that BDNF induces the expression of CRH *(Givalois 2004)* via the TrkB/CREB pathway *(Jeanneteau 2011)*. CREB (i.e., cAMP response element-binding protein) is a transcription factor which binds to cAMP response elements (CRE) and increases or decreases the expression of genes downstream of it, in this case CRH. Thus, the effects of BDNF on SPA may require increased activity of PVN CRH neurons activated by the TrkB/CREB pathway. This interaction is more complicated, because injecting BDNF into the PVN does not cause an increase in SPA *(Wang 2007)*. However, BDNF in the PVN does increase CREB, which in turn can increase the expression for CRH, yet this alone is not enough. Liu et al stated that phosphorylated CREB is essential but not sufficient for activation of CRH transcription *(Liu 2008)*. A missing link here may be inhibitory effects of glucocorticoids on the CREB regulated transcription coactivator 2 (CRTC2), which is a cofactor included in the BDNF-CRH pathway. CRTC2 has to be present in the nucleus to allow CREB to modulate CRH's expression *(Jeanneteau 2011)*, and high levels of glucocortiocoids would inhibit such an effect. Also, Zhou et al. have found that hippocampal cells treated with corticosterone have a reduced amount of mRNA expression for BDNF *(Zhou 2000)*. Thus, infusion of BDNF in the PVN may only increase SPA when glucocorticoid receptor (GR) feedback is relatively low. When BDNF fails to neutralize GR's inhibitory effect on the expression of CRTC2, BDNF's stimulatory effects in the PVN on SPA are inhibited.

The stimulatory effect of BDNF in the VMH to increase SPA may not require expression of CRH in this region, as this area of the hypothalamus has not been found to express CRH. Therefore, BDNF neurons may project to the PVN which causes upregulation of CRH in the PVN under specific conditions. It may, for example, be hypothesized that infusion of BDNF in the VMH decreases the GR expression in the PVN, thereby increasing the amount of CRTC2 in PVN neuronal cell bodies. Alternatively, CRH may be released into the neuropile to affect other CRH synthetizing regions and tissues, such as 1) the locus coeruleus, where CRH is colocalized in neuronal cell bodies, which project among other to hypothalamic regions (Sawchenko 1981), or 2) mast cells *(Kampuraj 2003)*. More research is needed into the relationship between BDNF and CRH to determine whether the TrkB/CREB signaling pathway is responsible for the increase of SPA.

Besides increasing EE by just increasing locomotion, there is an interesting side-effect. Skeletal muscle tissue also expresses BDNF, and this is increased after exercise *(Matthews 2009)*. The locally produced BDNF in the skeletal muscles does not enter the bloodstream *(Matthews 2009)*, thus would not ignite a positive feedback loop of BDNF increasing locomotion, which in turn increases BDNF, etcetera. Muscular BDNF does increase lipolysis in muscular tissue *(Pedersen 2009)*, which has a positive effect of breaking down fat storages for energy usage in muscular tissue. So not only does BDNF increase EE by stimulating SPA, it also breaks down fat reserves to fuel muscular activity.

Thermogenesis

Generation of heat is crucial for all warm-blooded animals. Humans and many other mammals, prefer and maintain a core body temperature of 37.5°C. Proteins perform their

function best in a relatively narrow range. 35°C is the minimal normal body temperature required for metabolic processes and other body functions, hypothermia occurs below this threshold. On the other end of the spectrum is hyperthermia. A body temperature over 41°C will cause most proteins to unfold, a process called denaturation. Unfolded proteins are unable to perform vital functions, and this will usually lead to cell death, and ultimately death of the individual. These two limits leave a rather narrow margin to sustain life in the face of large temperature fluctuations found in the environment. Yet we manage to maintain our body temperature within a few tenths of degrees Celsius. But how do we do this?

In order to keep warm the body generates its own heat, a process called thermogenesis. There are two types, shivering and non-shivering thermogenesis. Shivering thermogenesis, or just shivering, is caused by muscle contracting which generates heat. No functional movement is obtained because opposing muscle groups also contract. Non-shivering thermogenesis is thermogenesis caused by elevating the metabolic rate in a specific tissue, commonly occurring in brown adipose tissue (BAT) *(Tsuchida 2001)* in response to a cold environment *(van Marken Lichtenbelt 2009)*. To cool down the body can excrete sweat, reduce activity and increase the blood flow in extremities to increase heat dissipation. Central and peripheral heat-sensitive neurons provide information about the body temperature, and can signal specific nuclei in the brain.

The preoptic anterior hypothalamus (POAH) has been identified as the most important region when it comes to regulating body temperature *(Zhang 1995, Chen 1998)*. Thermogenesis of course occurs in most tissues; basically all energy from the body is finally lost as heat. BAT is probably the only tissue with non-shivering thermogenesis as its primary metabolic function. Thermogenesis in the BAT is regulated by norepinephrine (NE) *(Cannon 2004)* which stimulates expression of uncoupling protein 1 (UCP1) in its mitochondria. UCP1 is a transmembrane protein found primarily in mitochondria of BAT. UCP1 causes a proton leak in the membrane of mitochondria of adipocytes in BAT *(Cannon 2004, Matthias 2000)*. This leak renders transport over the membrane less efficient, effectively causing more heat to be produced. Mice lacking UCP1 show no increase of thermogenesis induced by NE *(Matthias 2000)*, so it seems UCP1 is necessary for NE to mediate thermogenesis in BAT.

BDNF has been shown to increase thermogenesis *(Wang 2007, Tsuchida 2001, Naert 2006, Nonomura 2001, Nakagawa 2000)*. Obese mice with a reduced body temperature will restore the body temperature to control values when given BDNF intracerebroventricularly *(Nonomura 2001)* and subcutaneously *(Nakagawa 2000)*. BDNF injected in rats induced an increase in thermogenesis when injected in the PVN *(Wang 2007)* and when infused with BDNF in the lateral ventricle *(Naert 2006)*. Animals under cold *(Tsuchida 2001)* or food restricted *(Nakagawa 2000)* conditions maintained their body temperature when injected with BDNF where control animals did not. The mechanism behind this appears to be an increase of UCP1 expression in BAT *(Wang 2007, Tsuchida 2001)*. NE turnover was also increased following BDNF administration *(Nonomura 2001, Tsuchida 2001)*. Interestingly, when BDNF is injected in the VMH the total EE increases significantly, but UCP1 expression in BAT remains unaltered *(Wang 2010)*. Body temperature was not measured in this study, but it is a possibility BDNF in the VMH increases EE by increasing thermogenesis in other tissues than BAT, such as skeletal muscle tissue. That stimulation of the VMH does little to affect thermogenesis in BAT is not surprising when you take into account that less than 2% of neurons in the VMH project to BAT *(Bamshad 1999)*. Thermoregulation via CRH is another possible mechanism. Intracerebroventricular CRH infusion leads to an increase in temperature in rats *(Linthorst 1997)*. As mentioned earlier, BDNF in the PVN increases the expression of CRH *(Givalois 2004)* which increases thermogenesis *(Givalois 2004, Wang 2007)*, as opposed to SPA. The expression of CRH in the PVN by BDNF is inhibited by glucocorticoids, e.g. cortisol. It has been shown that leptin, another important regulator of energy metabolism, fails

to alter FI, UCP1 expression and adiposity when an animal is simultaneously injected with a CRH-antagonist *(Masaki 2003)*. Studies using CRH antagonists simultaneously with BDNF might show whether this pathway plays a role. Finally, Gamma-aminobyturic acid (GABA) might be responsible for BDNFs alteration of thermogenesis. GABA is the main inhibitory neurotransmitter in the brain, and it reduces the sympathetic output of the PVN *(Chen 2005, DiMiccio 1986, Reddy 2005, Zhang 1998)*. BDNF has been shown to decrease the amount of GABA receptors *(Brünig 2001)*, and this may be hypothesized to be a possible mechanism behind BDNF's effect on thermogenesis.

Recent research by van Marken Lichtenbelt et al has shown that obese individuals have less active BAT *(van Marken Lichtenbelt 2009)*. It is present in 96% of the individuals studied, including the obese subjects, and this makes it a potential target for treatment. BDNF is an ideal candidate to treat this aspect of obesity, since it increases thermogenesis. Possible mechanisms of this are the upregulation UCP1 expression in BAT, increasing NE turnover in BAT or decreasing $GABA_A$ receptor number in BAT.

White to brown fat switch

Besides the already mentioned BAT, most of the body's adipose tissue is found as white adipose tissue (WAT). It is traditionally thought that WAT's function is energy storage, heat insulation and mechanical cushioning, but recent studies show additional functions *(Enerback 2009, Petrovic 2010, Seale 2008, Seale 2011, Cao 2011)*. WAT contains certain cells expressing UCP1, and these cells have the potential to mimic functions of BAT *(Enerback 2009, Petrovic 2010)*. These cells can be called brown-in-white (brite) cells, beige cells or adaptive brown adipocytes *(Enerback 2009, Petrovic 2010)*. These two types of adipose cells have a common precursor, with Prdm16 determining the BAT cell fate *(Seale 2008)*. Transgenic expression of Trdm16 in fat cells will induce brite cells in subcutaneous WAT *(Seale 2011)*, "browning" them. Research by Cao et al on mice suggested a possible way to "brown" these cells by enriching the environment *(Cao 2011)*. Enrichment of the environment can be achieved by increasing social interactions with conspecifics, interacting with novel objects and a running wheel. This enrichment was proven to be more effective in decreasing the adiposity of mice than running wheel access per se, while the enriched animals showed less total activity than the running wheel group *(Cao 2011)*. Even when the running wheel was removed from the enriched environment, these mice still decreased adiposity to a greater degree than the running wheel group *(Cao 2011)*. Food intake was either unaltered, or slightly increased in the enriched mice *(Cao 2011)*, suggesting the decrease in adiposity is caused by an increase in energy expenditure. The oxygen consumption showed differences between the enriched and running groups too; enrichment showed increased consumption in WAT, while running did so in BAT *(Cao 2011)*, indicating that the main place of effect of enrichment takes place in WAT. They proposed the transformation into BAT-like cells is responsible for this increase in EE, after seeing an increase of expression of Prdm16 in the WAT of enriched animals *(Cao 2011)*.

BDNF was implied in this mechanism since enrichment increases expression of BDNF *(Cao 2010)*. Hypothalamic overexpression of BDNF mimicked enrichment-induced "browning" of WAT *(Cao 2011)*. Administrating an antagonist of TrkB will reverse the enrichment-associated effects of BDNF *(Cao 2011)*. These effects are mediated by NE and their β adrenergic receptors. In WAT, enrichment increased sensitivity to NE stimulation by increasing the amount of β adrenergic receptors significantly; a 27-fold increase was found *(Cao 2011)*. Blocking the β-adrenergic receptors reduced "browning"-effects of enrichment and BDNF overexpression *(Cao 2011)*.

Which pathways lie downstream of the "browning" of WAT is unknown. Enrichment of the environment leads to an upregulation of CRH, but this is only temporary *(Cao 2011)*. It would be interesting to see if BDNF's upregulation of Prdm16 in WAT can be reproduced by infusing it into the PVN or intracerebroventricularly.

Food Intake

Nutrient quality and quantity are important aspects of energy metabolism. Recent increases in obesity have been linked to the growing ease of access to unhealthy food, and ingesting more calories than the body can spend. Thriving fast-food industries reflect the popularity of their unhealthy foods. The desire to eat is regulated in neuronal networks in the brain in response to peripheral factors. A well-known example of such a factor is leptin, a satiety signal originating from WAT, and its function is to decrease the food intake (FI) *(Hommel 2006)*. Interestingly, injection of leptin has been shown to increase BDNF levels in the VMH, indicating a role for BDNF *(Komori 2006, Xu 2003)*. The hypothalamic nuclei regulating food intake all express TrkB, further supporting the theory that BDNF plays a significant role in regulating FI. Indeed, a girl with a de novo mutation in the region encoding for BDNF showed severe obesity and hyperphagia *(Gray 2006)*.

BDNF has been shown to have a strong effect on food intake separate of this single case study. Infusing BDNF intracerebroventricularly reduces FI *(Pelleymounter 1995, Nakagawa 2003)*, which was quickly reversed after ending the treatment *(Pelleymounter 1995)*. Heterozygote mice displaying a reduced BDNF expression are hyperphagic *(Kernie 2000, Lyons 1999)*. Elimination of the BDNF gene after birth also leads to hyperphagia *(Rios 2001)*. FI was significantly decreased after injecting BDNF in the PVN *(Wang 2007)* and the VMH *(Wang 2007b, Wang 2010)*, indicating that both these areas are important for the regulation of FI. Subcutaneously injected BDNF in obese mice also managed to decrease FI when injected a single time *(Ono 1997, Tonra 1998, Nakagawa 2003)* or repetitively *(Ono 2001, Nakagawa 2000, Nakagawa 2003)*.

So there is a lot of evidence linking BDNF to the regulation of food intake. But the mechanisms behind this are still unknown. It is thought that the serotonergic system is involved. Serotonin is also known as 5-hydroxytryptamine and is popularly thought to be linked to mood. Studies have shown however that it is a regulator for FI, a central injection of 5-HT decreased FI significantly *(Curzon 1997)*. Lyons et al have shown that BDNF heterozygote and null mutant mice have a loss of 5-HT neurons after 12 months *(Lyons 1999)*. Also, administration of fluoxetine, a 5-HT uptake inhibitor, suppressed food intake in these hyperphagic heterozygous or null-mutant mice *(Lyons 1999)*. An uptake inhibitor reduces uptake of the molecule back in the cell, effectively increasing the exposure of the receptor to the molecule. The lack of BDNF during early stages of development causes abnormalities in the 5-HT system, which might cause the reduced FI in later stages of life. This however, does not explain the fact that FI was also reduced in the early stages of life (Lyons 1999). There is evidence that CRH is downstream of BDNF's action on FI. It has been pointed out earlier that BDNF increases the expression of CRH. Toriya et al. have shown that the reduction in FI following an intracerebroventricular infusion of BDNF is counteracted by simultaneous administration of alpha-helical-CRH, an antagonist for the CRH receptor *(Toriya 2010)*.

Another possible factor in the mechanism of BDNF is neuropeptide Y (NPY). NPY increases food intake and is highly expressed in the brain *(Mercer 2011)*. BDNF decreased NPY levels when it was injected in the VMH, and it also reduced the NPY-induced feeding *(Wang 2007b, Wang 2010)*. This effect also works the other way around; injection of NPY reduced BDNF levels *(Gelfo 2011)*. Therefore, a negative feedback loop between these two factors seems possible.

However, eating behavior in humans is not just regulated by the sensation of hunger and satiety. Food intake can be initiated for other reasons, for example to enhance mood, or by exposure to tasty food. Tasty snacks, like chocolate, sweets, or chips are perhaps the most unhealthy. Craving for snacks is regulated by the dopaminergic reward system and this system is therefore quite important when trying to find a treatment for obesity. Dopamine is released in the nucleus accumbens (NAc) and the prefrontal cortex via the mesolimbic pathway *(Bassareo 1997, Lee 2002)*. This pathway originates in the ventral tegmental area of the midbrain *(Bassareo 1997, Lee 2002)*. Many factors involved in appetite regulation use this system to regulate dopaminergic activity, like leptin, ghrelin and melanin-concentrating hormone (MCH) *(Hommel 2006, Fulton 2006, Abizaid 2006, Georescu 2005)*. Stimulation of these areas with microinjections leads to a dose-dependent increase of FI *(Mucha 2003, Noel 1995)*. Dopaminergic cells of this system express TrkB *(Numan 1999)*, implicating a role of BDNF. Mutant mice with decreased central BDNF showed significant decreases in dopamine release in the NAc and dorsal striatum *(Cordeira 2010)*. These mice showed en excessive increase of high-fat food intake, which was normalized by stimulation of the dopaminergic D1 receptor *(Cordeira 2010)*. Food intake was not altered for the standard chow food *(Cordeira 2010)*, so the lack of BDNF increases only the intake of palatable food by stimulating the dopamine system. Also, BDNF and TrkB expression in the VTA was decreased after ingestion of high-fat food *(Cordeira 2010)*. Collectively, a lack of BDNF makes it harder to resist tempting foods, resulting in a drastic increase of palatable food intake.

Conclusion

The fact that obesity is becoming a growing health concern might be due to the high availability of high fat foods, and the inability of people to resist them. High fat foods decrease BDNF levels *(Karczewska-Kupczewska, 2011)*, possibly leading to a vicious circle. This is supported by the fact that obese subjects have lower BDNF levels *(Krabbe 2006)*. The BDNF Val66Met polymorphism is quite common *(Pivac 2009, Zhou 2010)*. This SNP affects activity-dependent expression and signaling of BDNF *(Egan 2003)* and is linked to obesity *(Beckers 2008, Skledar 2012, Speliotes 2010)*. Also epigenetic mechanisms play a role because a recent study showed that BDNF production in the hippocampus was lowered in offspring of dietary obese mice (Tozuka 2010), indicating a programming effect of the mother towards the young.

It may seem possible to exploit BDNF as a marker for increased risk of obesity *(Rao 2008)*. Mandel et al have shown that BDNF is detectable in the saliva *(Mandel 2009)* and people with the Val66Met polymorphism had significantly less detectable BDNF in their saliva *(Mandel 2009)*. Administrating BDNF might be able to help them restore the balance in their intake versus expenditure. Data obtained from studies using injections or infusion directly in the brain, although instrumental in unraveling the actions of BDNF, do not necessarily broaden the applicability of BDNF as a target for the treatment of human obesity. However, subcutaneously injected of BDNF is able to pass the blood brain barrier *(Tsuchida 2001)*, offering a suitable method of administration. This method does require a higher dose to reach effect. A dose as infrequent as twice a week proved enough to decrease food intake and body weight in mice *(Ono 2000)*. Theoretically, an injection of BDNF twice a week is not too much of a burden for patients, especially when looking at alternative consequences. However, more research on human subjects has to be done, to see if administrating BDNF yields the same results as in animal models. Either way, BDNF appears to be a promising candidate in treating obesity.

In summary, BDNF is important for regulating energy balance by increasing energy expenditure and decreasing energy intake. On one side it increases energy expenditure by increasing the amount of spontaneous physical activity, possibly by increasing CRH expression and affecting sympathetic nervous system output towards BAT leading to an increase in resting metabolic rate. This effect is mediated by increasing the expression of UCP1 in BAT. An increase of thermogenesis separate from the BAT is triggered via CRH. Also BDNF has been implicated in causing a switch of WAT to BAT, but the mechanisms are still unclear. Energy intake is reduced by diminishing homeostatic food intake by hypothalamic BDNF, this effect may be due to the release of CRH into the system, or BDNF's inhibitory effect on NPY. But maybe the most relevant way BDNF decreases energy intake is by reducing the amount of palatable food ingested when it is available by acting on the dopaminergic system.

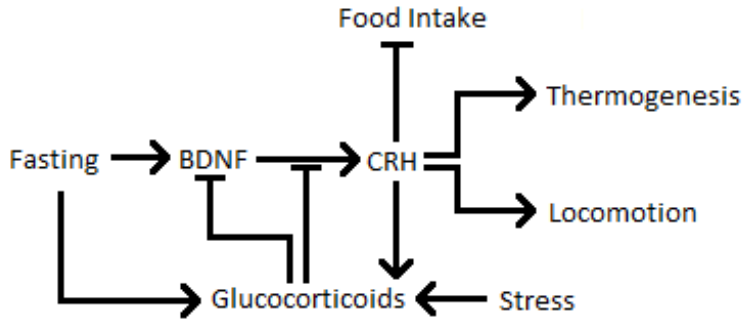

Fig.1.
BDNF's effect on energy balance via stimulation of CRH excretion is inhibited by GCs, as are BDNF mRNA levels. A negative feedback loop exists for CRH via GCs. Both stress and fasting are linked to elevated GC levels. The GC/BDNF interaction explains the increase of FI, reduction of locomotion and thermogenesis during fasting or stress.

CRH seems to be crucial for BDNF to perform its function. It is involved in BDNF's regulation of homeostatic feeding behavior, thermogenesis and locomotion. CRH stimulates the anterior pituitary to produce adrenocorticotropic hormone (ACTH), which in turn stimulates the release of corticosteroids. This includes the release of glucocorticoids (GC), which are synthesized in the adrenal cortex and act on the glucocorticoid receptor (GR). Glucocorticoids (GCs) prevent CRH formation via CREB, and reduce production of BDNF mRNA, as mentioned earlier. Thus a negative feedback loop exists for CRH. Despite the beneficial effects of BDNF and CRH, a constantly elevated BDNF level may obviously have negative consequences. Animals in the wild cannot afford to constantly have elevated energy expenditure. Escaping predation or other stressful environments will cost a lot of energy, which needs to be replenished. Stress is commonly known to be associated with excretion of glucocorticoids, such as cortisol. It's possible that this release is an important adaptation to allow for more effective reuptake of energy due to blocking of the effects of BDNF, by inhibiting CRH formation via CREB and by reducing BDNF mRNA. In this case, glucocorticoids may act as a brake on the BDNF system. Evidence for this brake is also found with fasting. Fasting will raise BDNF levels *(Qiu 2012)*, the main purpose of which may be to benefit from protective effects of BDNF on the brain. However, these animals cannot afford the increase in energy expenditure BDNF causes, and this is reflected by studies which show decreased thermogenesis and locomotion during fasting in mice *(Tannner 2010, Williams 2001, Koizumi 1992)*. Glucocorticoids are released following fasting *(Mager 2006, Patel 2002)*, allowing for high BDNF levels without the costly increase in energy expenditure by inhibiting CRH release. Therefore, this review theorizes that BDNF's main effector is found in CRH, and that glucocorticoids offer a brake on this system.

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