The sex differences in the association between stress and the reduced serotonergic system regarding to leptin insensitivity.

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The contents:

Abstract

Obesity is a growing problem and in 2017 more women than men struggled with this in The Netherlands. There is an important link between todays obesity and stress; a hormone involved in this is leptin. The research question of this article reads as follows: *''What is the association between stress and the serotonergic pathways regarding to leptin and how does it differ between males and females''*. The female hormone oestradiol underlies the increased leptin sensitivity in females and the presence of the male hormone testosterone decreases the leptin sensitivity directly. Besides the effects of the gonadal steroids on leptin, they also have an impact on the hypothalamus-pituitary-adrenal axis. Oestrogen has a stimulatory effect on the stress-induced HPA response and testosterone an inhibitory effect. People cope with stress using high fat food to reduce stress-induced decreased serotonin; and leptin reduces the serotonin pathway, as a mechanism to regulate the food intake. However, a greater fat food intake during stress is often associated with an increased leptin level, this could be caused by a lower sensitivity of leptin in the hypothalamus due to alteration of melanocortin pathway. From this paper, it can be concluded that besides the potential neuroprotective effect of oestrogen on the reduction of the serotonergic system due to stress, the female hormone also stimulates the stress induced HPA axis response. When the latter effect is greater, it can cause a leptin insensitivity and eventually obesity in females. This effect could be less in males while the testosterone tends to decrease the HPA axis response.

I. Introduction

Obesity is a growing worldwide problem. Nearly 14% of the adults in The Netherlands has obesity in 2017 and more women than men struggle with this problem. Overweight is officially called obesity, when the Body Mass Index is more than 30 kg/m2 (Centraal Bureau voor de Statistiek, 2018). Many people with obesity have mental health problems, because of the stress they experience. Important disorders are anxiety and depression (Scott et al, 2008). However, it is not clear whether obesity is the cause or a result of mental disorders. A study of Ouwens has suggested that depression directly effects emotional eating through ''difficulty of identifying feelings'' and ''impulsivity'' (Ouwens et al, 2009).

Stress has a major effect on the hypothalamus-pituitary-adrenal axis (HPA). Perception of stress, among via the hippocampus induces corticotropin releasing hormone (CRH) synthesis in the paraventricular nuclei (PVN) of the hypothalamus. Subsequently, CRH stimulates the pituitary which produces adrenocorticotropin (ACTH). As a reaction to this, the adrenals produce cortisol. Normally, cortisol, a glucocorticoid, is an essential part of the feedback mechanism of the HPA axis (Fig.1) (Brown et al, 1999). However, a high concentration of

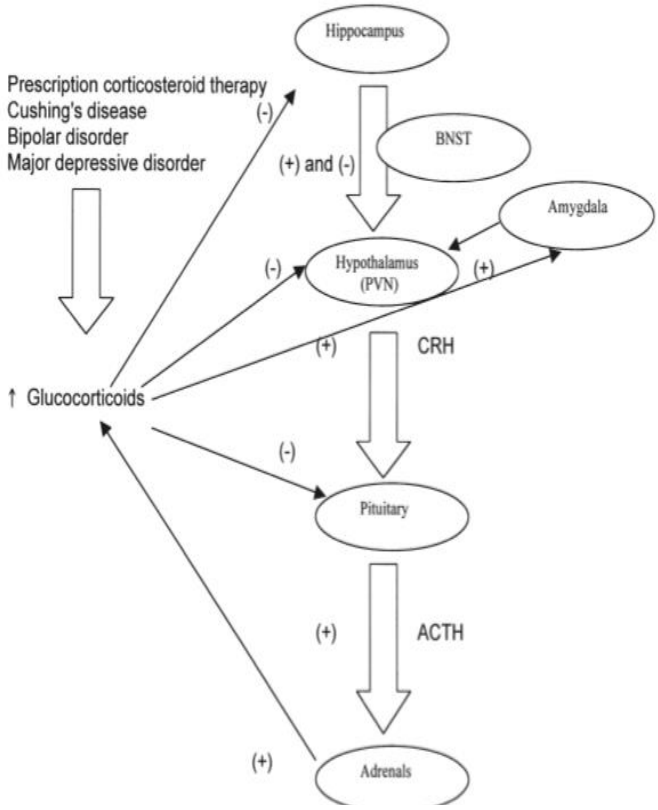

Figure 1. Brown et al, 1999

glucocorticoids during chronic stress destroys the negative feedback and leads to hyperactivity of the HPA axis (Zhu et al, 2014).

An important hormone which is involved in the link between obesity and stress is leptin, a product of the obesity gene. It has a significant role in metabolism as modulator of food intake. This ob protein supresses feeding in the ob/ob mouse, an obese model mouse, and it is secreted by the adipose tissue. A mutation in the ob gene of leptin causes obesity and type II diabetes. (Weigle et al, 1995 & Zhang et al, 1994). The leptin hormone not only causes a reduced food intake, but also an increased energy expenditure (Halaas et al, 1995). As demonstrated in the research of Heiman, leptin inhibits the release of CRH and is therefore an important feedback of the HPA axis (Heiman et al, 1997). Additionally, obesity causes leptin resistance via SOCS-3, a leptin-inducible inhibitor which decreases the leptin-STAT3 signalling pathway (Bjørbaek et al, 1998). The research of Considine has shown that obese people have a higher leptin concentration than normal-weight people and is thus correlated with the percentages of body fat. With this they conclude that obese persons are insensitive to leptin instead of having a leptin deviancy (Considine et al, 1996). This leptin resistance triggered by obesity can result in hypercorticism caused by the increased secretion of CRH (Heiman et al, 1997).

Moreover, Heiman speculates that leptin secretion decreases during chronic but also acute stress, which increases the HPA axis activity and is important in the survival during stressful situations (Heiman et al, 1997). In addition to the modulated effect of leptin on the HPA axis, leptin has also an effect on the reward system. An important association between serotonin, an important neurotransmitter in the reward system, and leptin has been demonstrated in several studies (Yada et al, 2018 & Yada et al, 2009). Furthermore, research have shown that the reward system might play an important role in the association between the increased intake of food and stress (Pijlman et al, 2003). Nonetheless, research suggested that there are differences between males and females (Krowlow et al, 2013).

The research question of this article is derived from this and it is as follows: *''What is the association between stress and the serotonergic pathways regarding to leptin and how does it differ between males and females''.*

II. Leptin and its mechanism

The human ob gene is present as a single-copy gene and is located on the 7q31.3 chromosome. The gene is a complex of three exons separated by two introns and made by the alternative mRNA splicing mechanism (Isse et al, 1995). The protein derivate of this gene is leptin and is expressed in the human adipose tissue, in specific the mature adipocytes. The amino acid sequence of this protein consists of 166 amino acid polypeptide and the ob mRNA level varied from region to region even in one individual (Masuzaki et al, 1995).

In the year of 1995, Tartaglia et al identified the Leptin Receptor, OB-R. They found a strong leptin binding in the mouse choroid plexus. Nucleotide sequencing showed a single membrane-spanning receptor with 894 amino acids. The extracellular domain of this receptor has a lot in common with the cytokine receptor family class I and has a transmembrane domain and short cytoplasmic domain attached. This research has also demonstrated that the receptor RNA is not only located in the choroid plexus but also in the hypothalamus (Fig 2.) (Tartaglia et al,1995). The leptin receptor has a few alternatively spliced forms, one of these is positioned in the hypothalamus. With this the research of Lee has already suggested in 1996 that the reduced food intake caused by leptin is mediated by signal transduction through the leptin receptors in the hypothalamus (Lee et al, 1996). Further research has discovered that the leptin

receptor gene is located in three important hypothalamic nuclei: arcuate, ventromedial and paraventricular. The spliced form of the leptin receptor in the hypothalamus is a receptor with a long intracellular domain, called the LRb (Mercer et al, 1996). This LRb receptor contains a mature extracellular domain of 816 amino acids long and intracellular domain of 303 amino acids (Fig.2) (Tartaglia et al, 1995 & Lee et al, 1996). The leptin receptor exerts its effect on the body energy homeostasis with STAT3 signalling and an interruption of the STAT3 signalling results in the leptin resistance.

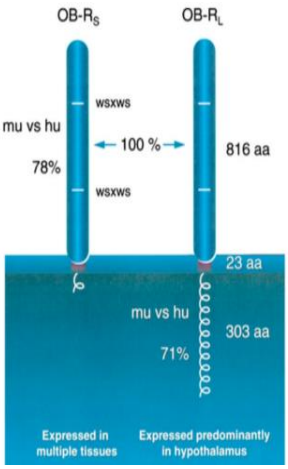

Figure 2 OB-R long form. The extracellular transmembrane and intracellular domain, schematically (Tartaglia, 1997).

A decreased LRb-STAT3 signalling could be involved in the leptin resistance which is a common mechanism in obesity. A possible reason for the obesity induced leptin resistance, is the impaired LRb-STAT3 signal in the arcuate nucleus which causes a lower activation of the hypothalamic POMC gene. At standard leptin receptor activation, this initiates the downstream pathway with the help of Y1138 phosphorylation site. In a response to this, the Jak2 tyrosine kinase gets activated with his downstream STAT3 phosphorylation and with this increases POMC production and finally α-MSH, α-melanocyte-stimulating hormone, and the melancortin MC3 and MC4 receptors. α -MSH is an agonist of the melanocortin receptors (Fig.3) (Bates et al, 2003 & Bjørbaek et al, 1997).

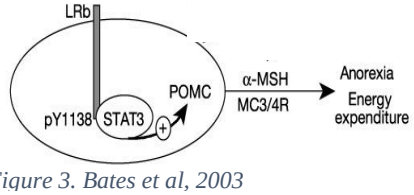

Figure 3. Bates et al, 2003

Additionally, the leptin hormone has a strong association with gonadal a... This was first observed in homozy... obese mice, in which this recessive g... initiates sterility in the mice (Ingalls et al, 1996).

III. The different leptin sensitivities determined by the two gonadal steroids oestrogen and testosterone.

An important distinction between the female hormone oestrogen and the male hormone testosterone is the sensitivity to the actions of leptin. The injection of leptin caused a greater reduction of food intake in female rats than in male rats. This anorexic effect still remained significant after 24 hours in females, this was not the case in males the leptin effect was no longer visible after 24 hours. The female groups had also lost a significant amount of body weight after the

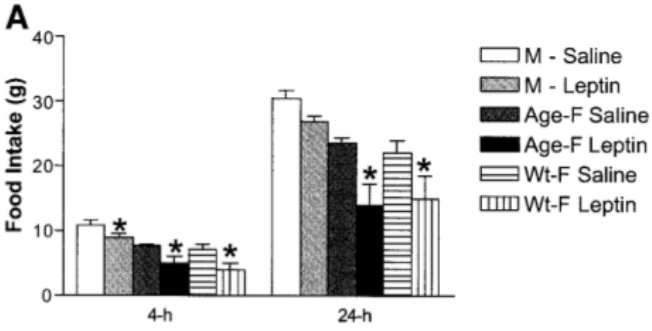

Figure 4. Female rats have a more decreased food intake than man after injection with leptin (Clegg et al, 2003)

24 hours (Fig.4). With these results it can be concluded that female brains are more sensitive to the actions of leptin then males. (Clegg et al, 2003).

An important downstream neuronal mechanism of leptin is the melanocortin system. After activation of the POMC gene α-MSH is formed, which is an agonist of melanocortin 3 and 4 receptors in, among others, the hypothalamus (Bates et al, 2003). To see if these sex differences are caused during the activation of the melanocortin

system, α-MSH is administrated in males and females. However, no difference in sensitivity was observed; the difference between sexes must occur with another mediator or more upstream (Clegg et al, 2003). To get a better view of the underlying mechanism of the sensitivity differences between males and females, Clegg manipulated the Gonadal hormones in both females and males. The animals were operated on beforehand: the ovariectomy (OVX) surgery in female rats to remove the ovary and oviduct and the castrations were performed on the male rats to remove the testis. Besides the castrated males and OVX females, there were sham operated males and females. These sham rats have been used as a control group. Administration of leptin reduced body weight and food intake in intact females, castrated males and males injected with oestradiol, however, not in intact males (Fig.5).

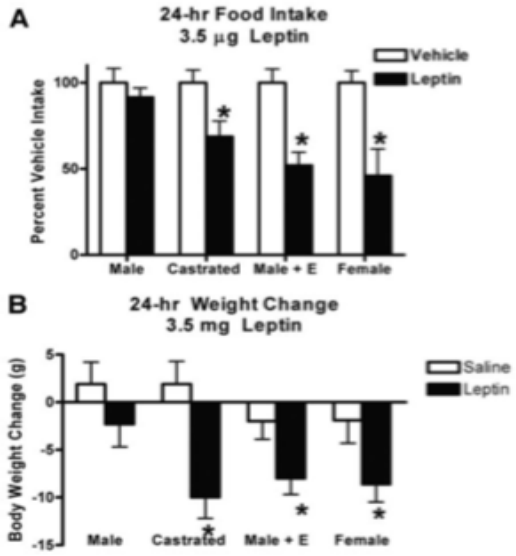

Figure 5. Adding leptin causes a reduction in intake and bodywieght in females, castrates males and estradiol treated males, but has little effect in intact males

Nevertheless, ovariectomy reduces the sensitivity to leptin independent of body weight compared to intact females, which had a reduced food intake after administration of leptin. Also, injection of oestradiol initiated a decreased food intake in response to leptin. Thus, leptin is more catabolic in the brain with the female hormone oestrogen compared to the situation without oestrogen and thus it is suggested that the female hormone oestradiol underlies the increased leptin sensitivity in females. Besides the increased leptin sensitivity, oestradiol also changes the body fat distribution. Males and OVX females, who received oestradiol intraventricularly and peripherally had significantly more subcutaneous fat than the control groups. OVX females without the administration of oestradiol had a reduction in oestradiol and an increased visceral fat accumulation. This could suggest that oestradiol signalling determines the amount of body fat through hypothalamic receptors (Clegg et al, 2006). These results are consistent with the difference in body fat distribution in male and female rats. Male rats have proportionally more visceral fat than females and females more subcutaneous fat (Clegg et al, 2006). Testosterone did not influence the leptin receptors in the hypothalamus directly, but the absence of this male hormone initiated an increased central leptin sensitivity (Clegg et al, 2006).

Besides the effect of oestradiol on leptin, the research of Diano detected a colocalization of the leptin receptors and oestrogen receptors in the hypothalamus. This indicated that the female hormone oestrogen acts through the same neuronal mechanism as leptin. With this information it is suggested that with this colocalization, leptin can affect the reproductive mechanism (Diano et al, 1998).

Not only oestradiol has an effect on the body fat distribution, but also the male hormone testosterone plays a role (Clegg et al, 2006). In 40-day old rats, the leptin concentration was greater in castrated males compared to the neonatal androgenized females, control females and the sham operated males. The reason for this could possibly be the absence of the neonatal

testosterone in male rats. Therefore, the manipulation of the androgen during the critical period of sexual differentiation (neonatal) causes long-term alterations of the leptin.

From these studies, it can be concluded that oestrogen increases the sensitivity of leptin and that testosterone indirectly decrease the leptin sensitivity by the presence of this male hormone (Clegg et al, 2006). Furthermore, it can also be concluded that testosterone supresses the leptin concentration after puberty in male humans and rats; and that leptin and testosterone are inversely correlated (de Mello et al, 2011 & Luukkaa et al, 1998).

Furthermore, there is an interdependence between the hormone systems of leptin and HPA axis (Heiman et al, 1997). Thus, with this, the next paragraph looks at the possible effects of leptin on stress and examines the possible mechanisms responsible for the differences between sexes.

IV. The effect of leptin on the HPA axis in females and in males.

Corticosterone, the rodent form of cortisol, is an important hormone of the HPA axis which also gives the HPA axis negative feedback (Brown et al, 1999). Research has shown that a high dose of leptin inhibits the stress-induced stimulation of ACTH and corticosterone. Besides the effects on ACTH and corticosterone, leptin inhibits also CRH release. Therefore, leptin is an important feedback mechanism of the HPA axis during stressful circumstances. Though, the inhibitory effect of leptin does not directly alter the ACTH release through the pituitary (Heiman et al, 1997).

Additionally, when looking at the involvement of the gonadal hormones the study of Handa et al has looked at the hormone effects in Foot Shock Stress in males. First, they looked at the effects of castration or substituted testosterone or oestrogen hormones on the ACTH and corticosterone secretion. The ACTH and corticosterone levels were augmented during foot shock in gonadectomized animals compared to control groups. Treatment with testosterone in the castrated males stopped the increase of post stress corticosterone and ACTH levels, causing ACTH and corticosterone levels to return to levels of intact males. Oestrogen treatment of castrated males caused a further increase in the post stress corticosterone levels; however, this effect was not visible in the ACTH levels. The effect of testosterone on the corticosterone receptors in the hypothalamus (i.e., as an index of the negative feedback sensitivity) did not reveal differences in the latter. However, there was no difference in the affinity of the receptors between the groups of this study. Thus, it was concluded that the effect of testosterone is mediated through a testosterone receptor mechanism instead of changes in the hypothalamic corticosterone receptor. Taken together, testosterone in male rats has an inhibitory effect the stress-induced HPA response, and this effect is not mediated through the corticoid receptors. Besides the inhibitory effect of testosterone, oestrogen in female rats has a stimulatory effect on the stress-induced HPA response. (Handa et al, 1993).

V. Stress increases the consumption of food and the sex differences of this effect.

Because of the association between stress and leptin, research has focused on the link between stress and the increased consumption in this society (Tataranni et al, 1996).

In 1996, Tataranni et al. already examined the effect of cortisol on food intake in healthy men. Their results suggested that administrating cortisol in healthy men would induce obesity by increasing food intake (Tataranni et al, 1996). Such an effect was found plausible by Zakrzewska et al. A continuous infusion of glucocorticoid in the central nervous system resulted in an

increased food intake, bodyweight and hyperleptinemia. Eventually, the administration of central glucocorticoids induced obesity. However, this induced obesity was not present when administrating peripherally. These results suggest that glucocorticoid induced obesity is via the central nervous system instead of peripheral (Zakrzewska et al 1999). The hyperleptinemia and obesity can be explained with leptin sensitivity. Administration of glucocorticoids may lower the leptin sensitivity via the central melanocortin system, the leptin downstream effector (Drazen et al, 2003). In females, the links between cortisol and body weight maintenance in females are less well understood. Subdividing females in a high cortisol reactivity group and a low cortisol reactivity group showed that the latter had a lower caloric intake than high cortisol reactivity group during the recovery of stressful days. On resting days no differences in caloric intake were found between high and low cortisol reactivity groups (Epel et al, 2011). On stress days, the intake of sweetened high fat food was significantly higher in the high cortisol reactors compared to the low cortisol reactors (Epel et al, 2011). Epel et al. also suggested that cortisol does not have a direct effect on the eating behaviour itself, but cortisol could modulate leptin sensitivity, which eventually has an effect on the eating behaviour (Epel et al, 2001).

Findings by Toniazzo et al. suggest that exposure to isolation stress in the prepubertal period can increased food intake in particular the high fat food diet on later age, indicating a preference of fat; men are more susceptible to chronic high fat diet and obesity. The increased consumption of high food intake was accompanied with increased leptin levels in both females and males (Toniazzo et al, 2018). The increase in leptin did not have a lower consumption and body mass as a result. On the contrary it was associated with an increased consumption. This could possibly be due the lower sensitivity to leptin in the hypothalamus (Toniazzo et al, 2018). The lower sensitivity can be the result of the SOCS-3 which blocks the leptin JAK-STAT3 pathway in the hypothalamus (Bjørbaek et al, 1998). The fact that phosphorylation of STAT3 was higher in stressed males, without an increase the SOCS3 levels suggests that the leptin signalling is impaired in another part of the pathway. In stressed females on the other hand, they found a decreased phosphorylation of STAT3 and an increased SOCS3.

Taken together, the various studies indicate that both in males and females an increased fat food intake during stress is associated with increased leptin levels; and that the reason for the contradiction could possibly be the lower sensitivity of leptin in the hypothalamus. However, the mechanism of the insensitivity differs between males and females (Fig.6) (Toniazzo et al, 2018).

Krolow et al assessed the long-term

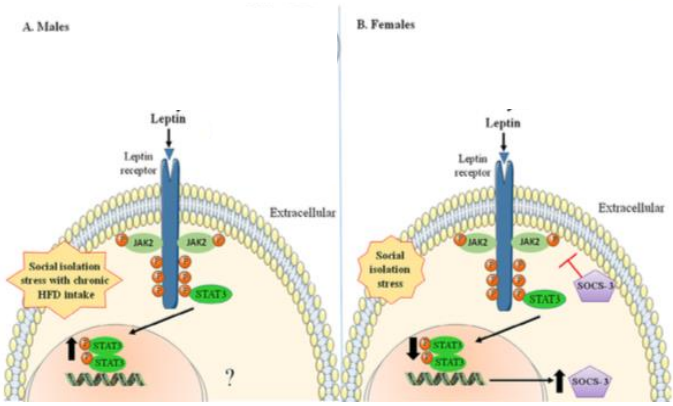

Figure 6. Leptin action in the hypothalamus of male and female rats influenced by social stress and High Food Diet intake (Toniazzo et al, 2018).

effects of stress and found an increased adrenal weight in adult male rats due to prepubertal stress, the adrenal weight in adult female rats did not change. This could indicate that female rats adapt more easily or cope better with stress over time than males (Krolow et al, 2013).

The high preference for a high fat diet previously indicated could be caused by the increased sensitivity to reward due to the

emotional stress. This was not the case in physical stress, for example foot shock, which causes an incapability to feel pleasure in pleasurable situations (Pijlman et al, 2003). In addition to the reward system, Buwalda et al investigated the responses of stress affected by high-fat feeding in male rats. They suggested that a high fat diet may reduce the negative effects of social stress on the serotonergic system (Buwalda et al, 2001). Thus, with this it is suggested that to cope with chronic stress, people use high fat food as a form of comfort food to reduce the stress-induced decreased serotonin level (van Dijk et al, 2008).

VI. The effect of leptin on the alterations of stress-induced serotonergic system caused by comfort food.

Leptin has been shown to induce inhibition of the serotonin pathway in arcuate neurons of the hypothalamus, as a mechanism of leptin to regulate food intake (Yadav et al, 2018). Serotonin is a product of tryptophan hydroxylation (Hamon et al 1981 & Patel et al, 2004). Tryptophan hydroxylase 2 (TPH2), the enzyme of tryptophan which catalysed the hydroxylation, is found exclusively scattered throughout the raphe nuclei. With this information it is likely to say that the expression of TPH2 causes the transcriptional regulation of serotonin synthesis (Patel et al, 2004). Serotonin exerts its effect on the attenuation of the appetite through signals on the Pomc-expressing neurons via Htr1a and Htr2b, the two serotonin receptors in the arcuate neurons of the hypothalamus (Fig 7.).
In those Pomc-expressing neurons CREB signalling regulates food intake due to its transcriptional effect which affects expression of genes that modulate appetite. This activity in the arcuate neurons is under control of leptin and serotonin (Patel et al, 2004).

Secondly, the association between the leptin receptor and serotonin is further explained by the finding that ObRb, the long form of leptin receptor, is co-expressed in β-galactosidase positive TPH2 expressing neurons. The TPH2 expression and serotonin is increased in ob/ob mice. Data has demonstrated that leptin induces reduction of action potential frequencies in serotonin neurons in the wild type mice. However, this was not the case in mice with absence of the ObRb in the TPH2 neurons. Thus, leptin can directly alter the serotonin levels through ObRb activation in TPH2 neurons (Fig.8) (Yadav et al, 2009).

As mentioned, organisms cope with stressful situation with consuming comfort food (van Dijk et al, 2008). The melanocortin pathway, the downstream factor of leptin, has been shown to play an important role in the link between the increased high fat diet and the altered leptin. Leptin activates neurons in the hypothalamus which eventually leads to α-

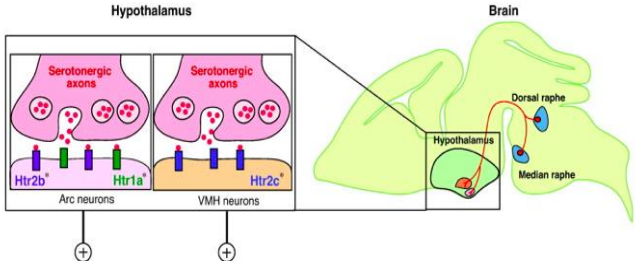

Figure 7. Serotonin binding to the Htr2b and Htr1a receptors in the arcuate neurons of the hypothalamus causes appetite (Oury et al, 2011).

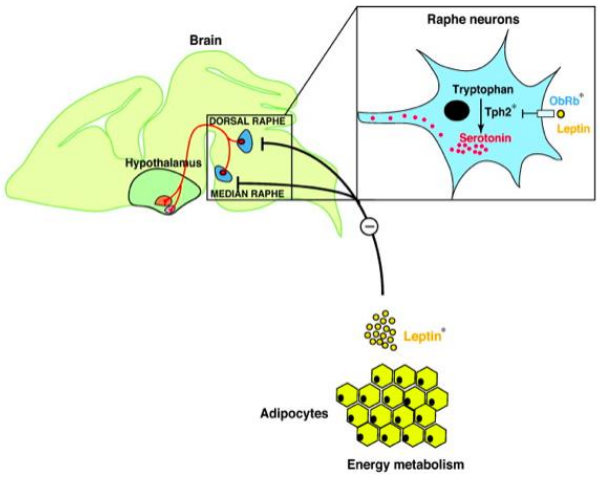

Figure 8. Leptin directly inhibits serotonin synthesis and serotonin release; this effect is mediated with ObRb.

melanocyte stimulating hormone and melanocortin receptors (Bates et al, 2003 & Bjørbaek et al, 1997). A pharmacological antagonist of these melanocortin receptors increases the visceral adiposity in animals, this adiposity is further increased with the consumption of high-fat diet; this was not the case in rats without the antagonist. With this Morens et al concludes that the melanocortin signalling is further impaired due to the high consumption of high-fat diet and eventually leads to obesity (Morens et al, 2005).

However, the reduced melanocortin activity due to the high-fat diet could potentially also be seen as an important anti-depressive which could ultimately reduce emotional consequences of stress. This anti-depressive effect is mainly caused by the MC4 receptors and is demonstrated with the MC4 receptor antagonist (Chaki et al, 2007).

VII. The alterations of the serotonergic system and leptin in females and males.

Intra-abdominal fat seems to be stimulated by the HPA axis overactivity due to stress. Thus, there is a correlation between the cortisol accumulation and an increased level of intra-abdominal fat. (Björntorp, 1993).

Weber-Hamann et al found an accumulation of visceral fat in hypercortisolemic depressed patients, this was not the case in normocortisolemic depressed patients; thus, increased cortisol levels may play an important part in the accumulation of fat. However, they suggest that hypercortisolemia is not the only cause of the intra-abdominal fat accumulation. The reason for this finding, is the fact that there were no differences in visceral fat accumulation between the hypercortisolemic depressed patients and normocortisolemic control subjects.

So, besides cortisol there is another important factor that regulates fat accumulation. Alterations in gonadal steroid concentrations are considered as relevant in postmenopausal women. With this the conclusion has been drawn that endocrine alterations due to depression is relevant in the deterioration of the physical health and fat accumulation in patients (Weber-Hamann et al, 2002).

A mechanistic link between intra-abdominal fat and depression could be the serotonergic system. This has been tested in the research of Homberg et al. They have used SERT -/- rats which have a depression-prone serotonin transporter knockout. SERT functions as a 5-HT reuptake site, which results in an extinction of the serotonin receptor stimulation. Thus, the deficiency of SERT causes a higher serotonin level. The results have suggested an accumulation of the intra-abdominal fat in serotonin transporter deficiency, this was only present in female rats. However, the bodyweight did not increase in the SERT -/- female rats, which indicates that the increased abdominal fat in depressed females occurs without significant bodyweight alterations. The sex-specific outcomes may be due the gonadal steroids, in particular the hormone oestrogen (Homberg et al, 2009). The oestrogen levels could stimulate adipose tissue deposition (Homberg et al, 2009 & Pallottini et al, 2008).

The overall activity of the HPA axis was reduced in the SERT knockout mice (SERT-/-), this was proven with the demonstrated reduction of CRF expression. This decrease in CRF may have an upregulation of CRF type 1 receptor as a result, which increased the function and the density of this receptor in the pituitary. This upregulation of the CRF type 1 receptor caused by a decreased CRF expression was not the case in partly reduced SERT expression mice (SERT+/-). On the contrary, in those mice the CRF type 1 were reduced in the pituitary.

In conclusion, the knockout of the SERT mechanism can result in antidepressant effects, caused by the higher

serotonin levels. This could be the cause of the decreased CRF expression.

VIII. Discussion.

While obesity is a common phenomenon in today's society, research has been carried out to demonstrate the possible link between stress and obesity (Centraal Bureau voor Statistiek, 2018 & Scott et al, 2008). The important mechanism of stress is the HPA axis with Glucocorticoids as feedback mechanism. However, a high concentration of this stress hormone results in a destroyed feedback (Zhu et al, 2014).

The adiposity hormone, leptin, is probably involved in the link between stress and obesity (Weigle et al, 1995). Its main task is reducing the food intake and increasing the energy expenditure mediated by its receptor, OB-R, in the hypothalamus. (Lee et al, 1996 & Halaas et al, 1995). Leptin sensitivity differs between males and females; oestrogen increases the sensitivity of leptin directly and testosterone decreases the sensitivity indirectly (Clegg et al, 2006). Leptin is involved in another mechanism besides metabolism, it inhibits the stress-induced stimulation of ACTH and corticosterone (Heiman et al, 1997).

Testosterone has an inhibitory effect and oestrogen has a stimulatory effect on the stress-induced HPA response (Handa et al, 1993). As mentioned above, there is a correlation between food consumption and stress. People with a high cortisol level have a higher food intake on stressful events (Epel et al, 2001). The increased food intake is often accompanied with increased leptin levels in males and females. However, the greater leptin levels did not have a lower consumption effect; on the contrary, it increases the consumption. This could be due to the lower sensitivity of leptin in the hypothalamus, the mechanism however differs between sex. Moreover, research has demonstrated that people cope with stress with an increased consumption of food. An important hormone in this coping behaviour is serotonergic system which is reduced due to stress (Buwalda et al, 2001). Nevertheless, in order to regulate the food intake, leptin inhibits the serotonin levels in the hypothalamus (Yadav et al, 2018). Leptin exerts its effect on serotonin directly with the long form of the leptin receptor, which is located in the β-galactosidase positive TPH2 expressing neurons (Yadav et al, 2009). An important peptide hormone in the decreased leptin levels and increased high fat diet is Melanocortin. This downstream factor is impaired due to the high consumption and eventually leads to obesity (Morens et al, 2005).

Additionally, also the alterations of serotonin and leptin differ between females and males. Only female mice with a SERT deficiency had intra-abdominal fat accumulation (Homberg et al, 2009). SERT knock out can cause antidepressant effect, because it cannot exert its effect on the serotonin reuptake causing a higher serotonin (Homberg et al, 2009). Another research has already shown a neuroprotective effect of oestrogen in Schizophrenia (Seeman et al, 1990). Oestrogen exerts its neuroprotective effect on schizophrenia through its effects on the serotonin receptor (Gogos et al, 2006). I think this could be also the case in stress-induced reduction of serotonin. Nevertheless, if oestrogen has a protective effect, how could obesity be more common in females than in males? Besides the neuroprotective effect of oestrogen on serotonin, it also has a stimulatory effect on stress-induced HPA axis response. A higher cortisol level, caused by the increased HPA axis response, could cause an increased food intake with an increased leptin concentration. Even though oestrogen increases the sensitivity of leptin, an increased leptin concentration in combination with a higher food intake can indicate a leptin insensitivity. In females, this could be caused by an augmented inhibitory effect of SOCS-3. Research has shown that this inhibited effect is largely

caused by social isolation stress (Toniazzo et al, 2018). Normally, leptin inhibits the stress-induced stimulation of ACTH and corticosterone, however, with leptin insensitivity this effect disappears. The increased cortisol concentration due to oestrogen and leptin insensitivity can also destroy the negative feedback of itself, this could lead to a hyperactivity of the HPA axis; and eventually more cortisol. Additionally, the increased food intake due to the leptin sensitivity can cause an even more severe obesity (Fig 9.). A promising reason for the less common obesity in males could possibly be due to the inhibitory effect of testosterone on the HPA axis.

Altogether, besides the possible neuroprotective effect of oestrogen on the stress-induced reduction of the serotonergic system, oestrogen also stimulates stress-induced HPA axis response. That stimulatory effect could be greater than the neuroprotective effect, causing a leptin insensitivity and eventually obesity in females (Fig 9.). This effect could be less in males because testosterone results in a decreased HPA axis response.

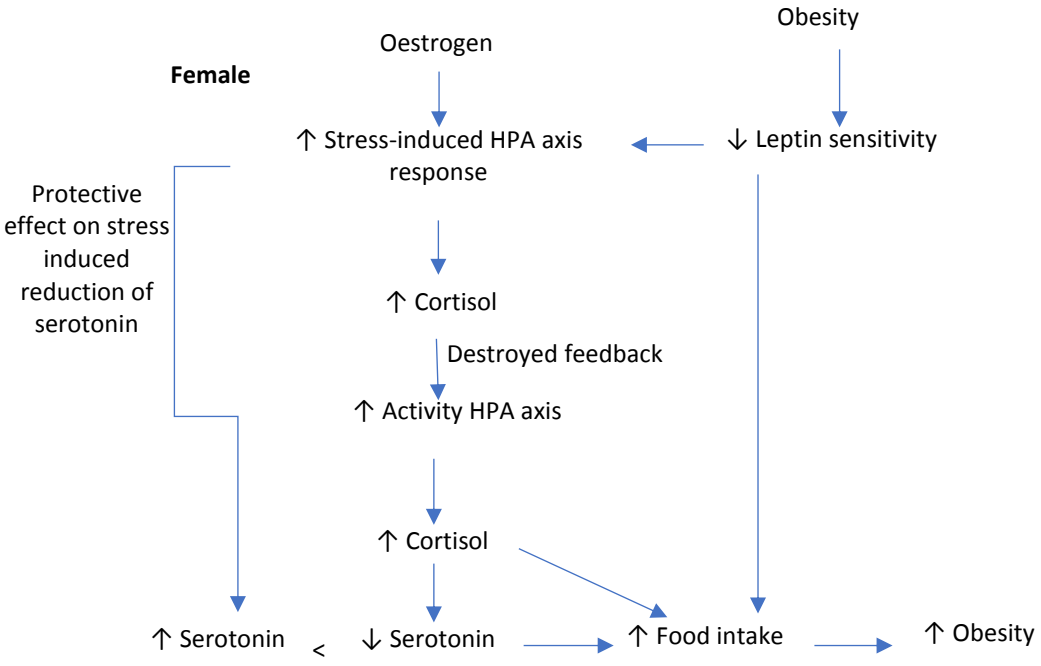

Figure 9. Effects of oestrogen and leptin insensitivity in female.

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