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# Metabolic syndrome: Aggression control mechanisms gone out of control

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SUMMARY

An upcoming hypothesis about the evolutionary origins of metabolic syndrome is that of a 'soldier' to 'diplomat' transition in behaviour and the accompanying metabolic adaptations. Theoretical as well as empirical studies have shown that similar to the soldier and diplomat dichotomy, physically aggressive and non-aggressive strategists coexist in animal societies with negative frequency dependent selection. Although dominant individuals have a higher reproductive success obtained through means such as greater access to females, subordinate individuals have alternative means such as sneak-mating for gaining a substantial reproductive success. The alternative behavioural strategies are associated with different neurophysiologic and metabolic states. Subordinate individuals typically have low testosterone, high plasma cholesterol and glucocorticoids and elevated serotonin signalling whereas dominant ones are characterized by high testosterone, low brain serotonin and lower plasma cholesterol. Food and sex are the main natural causes of aggression. However, since aggression increases the risk of injury, aggression control is equally crucial. Therefore chronic satiety in the form of fat should induce aggression control. It is not surprising that the satiety hormone serotonin has a major role in aggression control. Further chronically elevated serotonin signalling in the hypothalamus induces peripheral insulin resistance. Meta-analysis shows that most of the anti-aggression signal molecules are pro-obesity and pro-insulin-resistance. Physical aggression is known to increase secretion of epidermal growth factor (EGF) in anticipation of injuries and EGF is important in pancreatic beta cell regeneration too. In anticipation of injuries aggression related hormones also facilitate angiogenesis and angiogenesis dysfunction is the root cause of a number of co-morbidities of insulin resistance syndrome. Reduced injury proneness typical of 'diplomat' life style would also reorient the immune system resulting into delayed wound healing on the one hand and increased systemic inflammation on the other. Diabetes is negatively associated with physically aggressive behaviour. We hypothesize that suppression of physical aggression is the major behavioural cue for the development of metabolic syndrome. Preliminary trials of behavioural intervention indicate that games and exercises involving physical aggression reduce systemic inflammation and improve glycemic control.



## Introduction

The metabolic syndrome comprising insulin resistance, central obesity, type 2 diabetes, hypercholesterolemia, hypertension, atherosclerosis and coronary artery disease is considered a lifestyle disorder. However, the evolutionary origins of this syndrome are debated. The long standing hypotheses of thrifty gene [1] and thrifty phenotype [2] or epigenotype [3] have been challenged on several grounds and alternatives are suggested [4–8]. Some of the critics of thriftiness family of hypotheses have completely rejected the concept [4,5], whereas others have pointed out the inadequacies of the hypotheses and suggested alternatives which are not incompatible with thriftiness hypotheses [6,9]. One of the alternative hypotheses which says that the metabolic changes are adaptive to a 'soldier' to 'diplomat' transition in lifestyle appears to explain most of the metabolic, immunological, reproductive and cognitive changes known to accompany insulin resistance [6,9]. Belsare [10] pointed out that this Watve–Yajnik hypothesis can account for thriftiness and that thriftiness can be

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a subset of the hypothesis. The hypothesis also accounts for fetal origins of metabolic disorders [6]. However, certain questions remain unanswered and some scepticism on the Watve–Yajnik hypothesis is possible. It can be argued that the 'soldier' and 'diplomat' are typical human traits of fairly recent cultural origin. Therefore whether there has been sufficient evolutionary time to evolve physiological switches for such responses is questionable. Secondly the molecular mechanisms that convert a soldier to diplomat transition into insulin resistance are also not well elucidated so far. In this paper we refine and reshape the Watve–Yajnik hypothesis and further argue that alternative behavioural strategies parallel to the 'soldier to diplomat' metaphor are commonly present in animal societies and that the neuro-endocrinological and metabolic changes accompanying these strategies can explain insulin resistance and accompanying disorders.

In a wide variety of species males compete for females and mating behaviour necessitates aggression and dominance. However males that are weak, submissive or subordinate are not complete reproductive failures. In a wide variety of species subordinate males remain with the harem submissively and sneak-mate opportunistically [11–14]. Thus two alternative male mating strategies can coexist and be differentially successful. Game theory has shown that aggressive and submissive, i.e. 'hawk' and 'dove' strategies can coexist at a stable equilibrium in a population [15]. Selection for 'hawk' or 'dove' strategies is negatively frequency dependent, i.e. in a population predominated by doves, hawks have a greater fitness advantage and vice versa. There is some evidence that even in human societies the contribution of physical aggression to reproductive success is negatively frequency dependent. The reproductive success of aggressive individuals was greater than submissive ones in the Yanomamo societies but was lower in the Waorani tribe where the frequency of aggressive encounters was much higher [16]. A more complex example of coexistence of alternative strategies is that of lizard males with small territories, those with large territories and those without territories that coexist in a rock–paper–scissor like game [17]. These empirical studies and theoretical models imply that negative frequency dependent selection on two or more alternative ways of gaining success can lead to genetic polymorphism in a population. This is important because one major criticism of the thrifty gene hypothesis can be that the presumed selective advantages of thriftiness would result in directional selection making every individual 'thrifty' and polymorphism is an unlikely outcome, whereas selection for soldier–diplomat or hawk–dove strategies can theoretically lead to a stable polymorphism.

Alternative strategies work not only for mate competition but also apply to food access, stress response and other factors. For example while stronger and dominant individuals fight for a patch of food, the submissive ones may wait and watch for opportunities to sneak. Two distinct classes of coping strategies are demonstrated in rodents in which the aggressive strategists show an active response to stress situations and in situations of defeat they react with flight or escape. On the other hand the non-aggressive strategists are passive and in aversive situations react by immobility and withdrawal rather than flight and escape [18]. The 'hawk–dove' dichotomy in animals has many parallels as well as some important differences with the 'soldier–diplomat' dichotomy in humans. Both 'doves' and 'diplomats' avoid physical confrontation. Both need to be socially smart and opportunistic and thereby compensate for physical subordination. However there are two important differences between 'doves' and 'diplomats':

(i) In animal societies subordinate individuals generally have a lower social status. Patches of richer food are more likely to be snatched by dominant individuals leaving the subordinate ones with less calorie rich food. Since subordinate individuals are likely to have less as well as insecure access to food, they need to develop a "thrifty" metabolism and indulge in binge eating. Social subordination is shown to induce high fat intake and weight gain in animals [19] and this would be adaptive for individuals who have only occasional access to rich food. Unlike 'doves' in animal societies, 'diplomats' in modern human societies can have higher social status and continued access to calorie rich food. The high calorie availability for physically weak and inactive individuals poses a paradox that is characteristically human and more typical of modern lifestyle.

(ii) Physical aggression is the only predominant form of aggression in animals whereas verbal and political aggressions are alternative forms of aggression in humans. The metabolic requirements of the different forms of human aggression are likely to be much different. In our hypothesis below we use the term aggression to imply predominantly physical aggression. Verbal and political aggressions are assumed to be components of 'diplomat' rather than 'soldier' strategy.

Despite the two important differences, the close parallels between animals and humans in the behavioural dichotomy imply that metabolic adaptations accompanying behavioural shifts speculated by the Watve–Yajnik hypothesis could have arisen very early in evolution.

A number of studies have shown that diabetic rats show loss of aggression and increased submissive displays (review [20]) fitting well with the soldier–diplomat paradigm. It is difficult to infer from human data unless we clearly distinguish between physical and verbal aggression and not all studies make a clear distinction. However, a number of observations are compatible with animal experiments. Social subordination or low decision-latitude is shown to increase the risk for type 2 diabetes [21], low cholesterol levels are associated with aggression [22,23], aggression suppression increases the risk of hypertension [24–26] and people negatively associate physical aggression with abdominal and overall obesity in a 'body reading' test [27]. Of particular interest is the record that incidence of diabetes was reduced during World Wars I, II [28,29] and other long drawn wars such as the Sarajevan war [30]. In Sarajevo, during war time the percentage of hypertensive adults decreased and a large proportion of type 2 diabetic patients showed improved glycemic control without any medication [30]. All these studies attribute the improved epidemiological picture to dietary changes during war, but no data on dietary changes are given in support. It is equally likely that the war induced 'soldier' attitude could have played a role. These indications necessitate that the relationship of physical aggression and dominance with insulin resistance syndrome be examined carefully.

## Hypothesis

We hypothesize that loss of physical aggression, which accompanies the 'soldier' to 'diplomat' transition, is central to the development of type 2 diabetes and other components of the metabolic syndrome. The molecular machinery of aggression control induces insulin resistance and insulin resistance helps shifting the energy budget allocation from muscles to brain to support a physically submissive but socially smart lifestyle. In addition aggression suppression is accompanied by disinvestment in peripheral innate immunity, wound healing and angiogenesis mechanisms since injuries are less likely. This transition in metabolic and immune states accompanying a soldier to diplomat transition evolved as an adaptive response, however, the extreme non-aggression and non-injury-proneness that characterizes modern lifestyle brings about an exaggerated body response that turns pathological.

*Detailed description of the hypothesis*

Food and sex are the two major causes of aggression. Other causes such as territoriality, social ranking, self defence, mate guarding, maternal aggression are all related to the two basic needs of food and reproduction. Effective aggression can result into more access to food or better mating opportunities. However, aggression has an energetic cost as well as increased risk of getting injured. Therefore when there is no need for aggression or aggression is unlikely to be effective it has to be controlled. A satiated individual does not need to be aggressive and therefore cues of food satiety such as physically having a stomach full, high blood glucose or energy reserve in the form of fat should signal aggression control. Sexual satiety is also expected to arrest aggression and there is evidence that the underlying hormonal mechanisms are similar [31,32]. In human females, after menopause one major natural cause of aggression is eliminated and the body is predisposed to insulin resistance. In men although there is no clearly defined age of sexual senescence a strong positive association between sexual activity and insulin sensitivity is expected. In primate societies dominant males have greater access to females but their dominant position is under a continued threat and therefore they have a short but intensive sex life unlike subordinate males. For subordinate individuals, since, the number of opportunities of reproduction are less, they have to make the best use of available opportunities and therefore invest more resources, energy and efforts towards each offspring. This leads to a shift from an 'r' like reproductive strategy to a 'K' like reproductive strategy [6].

If rival individuals are stronger, then aggression is less likely to be effective or can even be counterproductive and therefore there is a need for aggression suppression. Thus physically weaker and subordinate individuals need greater control or suppression of aggression. If the frequency of aggressive encounters is high, inter-aggression intervals would be too short for healing and under such conditions the cost of minor injuries can also be high. The frequency of encounters can be high at high population densities and therefore high population density should trigger mechanisms of aggression suppression. Chronic crowding has been shown to decrease aggression in mice as well as primates [33–35]. In a number of rodent experiments isolation is used to induce aggression [36–40]. Therefore increase in the prevalence of metabolic syndrome in crowded environments [41,42] should not be a surprise. Thus it appears that the four main signals for aggression suppression namely: (i) acute or chronic food satiety, (ii) deterioration of sexual motivation, (iii) weaker physique and subordinate status and (iv) high population density are all risk factors for metabolic syndrome.

In order to utilize the alternative strategies of success the physically weaker individuals need to be smart and opportunistic. Therefore aggression control needs to be accompanied by mechanisms of enhancing cognitive brain functions. Thus there could be a trade off between physical strength and aggression versus social manipulation skills. In humans simple "retreat" like physical movements have been shown to enhance short term cognitive performance [43]. The principle of parsimony generally followed by biological systems implies that there should be disinvestment from organs and functions that are less frequently used. Non-aggressive lifestyle is expected to be accompanied by disinvestment in muscle and bone strength. The reduced injury-proneness accompanying diplomat lifestyle is also expected to reorient the immune system. The normal migration of neutrophils and macrophages from blood stream to peripheral tissues stimulated by frequent minor injuries should be reduced to achieve parsimony. The secretion of chemokines by adipocytes is a likely mechanism of arresting phagocyte migration [9]. Phagocytes migrate under a chemokine gradient that is formed by the difference between local and basal levels of chemokines. Chemokine secretion by adipocytes increases the basal levels thereby weakening the gradient. A mathematical model by Watve and Mandani [9] showed that even a small increase in basal chemokine levels can result in substantial reduction in cell migration. In diabetic patients the concentration of the monocyte–macrophage lineage is known to increase in adipose tissue [44,45] and blood vessels [46] and decrease in peripheral tissues [47]. Further the increased baseline levels of cytokines chronically activate phagocytes accumulated in vascular tissue resulting into vascular inflammation proneness which is mainly responsible for micro [48–50] and macrovascular diseases [51–53]. Further there could be disinvestment from wound healing and angiogenesis mechanisms as well. Most of the pathological consequences of metabolic syndrome seem to arise from the immune reversal and disinvestment in wound healing and angiogenesis mechanisms. Angiogenesis dysfunction is mainly responsible for diabetic nephropathy [54,55] and retinopathy [56,57]. It has been argued that type 2 diabetes is primarily a vascular disorder, only secondarily and lately reflected in hyperglycemia [58]. The major sources of free radicals in the body are the phagocytic cells of the body, which use them to fight infections. The immune redistribution increasing the density of phagocytes in central circulation and their chronic activation by increased basal levels of cytokines leads to oxidative stress which is responsible for a variety of tissue damages. The origin of oxidative stress therefore appears to lie in the immune redistribution accompanying a non-injury-prone lifestyle. The pancreatic beta cells are particularly more vulnerable to oxidative damage [8,59,60]. Thus it can be seen that most of the known mechanisms of pathogenesis in metabolic syndrome stem from the suppression of aggression and accompanying disinvestments in peripheral immunity and angiogenesis.

The hypothesis thus visualizes two behavioural strategies each one with its characteristic set of intercorrelated physiological states. One is the insulin sensitive strategy, that of a physically strong, dominant, active and aggressive individual accompanied by intense sexual activity, more peripheral distribution of immune cells and lower oxidative state. The other is the insulin-resistant strategy, that of a physically subordinate but socially smarter individual accompanied by disinvestment in bone and muscle, increased investment in brain and its cognitive functions, restrained sexual desire and altered distribution of immune cells resulting into increased systemic inflammation and oxidative stress.

It is likely that the cues for physically aggressive life style at least partially come from the neuro-motor actions involved. The modern lifestyle saw an overall decreased frequency of aggressive neuro-motor actions and reduced injury proneness. Even violence in modern life may involve operating a trigger of a gun which may not be recognized as a violent neuro-motor action by the body evolved for a hunter–gatherer life. The extreme form of withdrawal from physical aggression typical of modern urban lifestyle may be resulting in an exaggerated response making an adaptive change pathological.

*Molecular mechanisms of the transition*

The endocrinology of territorial aggression and dominance in animals is well known. Dominant and physically aggressive individuals have high testosterone/estradiol levels and both testosterone and estradiol are known to have a protective role in the metabolic syndrome [61–65]. Serotonin, on the other hand is important in the control or suppression of aggression. In a wide variety of species manipulated elevation of serotonin levels change the dominant status of individuals [66–70]. Subordinate individuals also have higher basal corticosterone [71–74] and higher plasma glucose [75]. A transition from soldier to diplomat must be

accompanied by control of physical aggression on the one hand and increased social manipulation skills on the other. In agreement of this, serotonin is important in cognitive functions of the brain [76–79], but it impairs spatial working memory [80] a critical need of a hunter or warrior. Insulin resistance is a strategy that shifts energy allocation of the body from muscle to brain. The reduced uptake of glucose by muscles in insulin resistance makes more of it available to the brain whose glucose uptake is independent of insulin action [6]. Also hyperinsulinemia is known to enhance cognitive functions of the brain [81]. Chronically increased serotonin signalling in the hypothalamus is shown to induce insulin resistance [82,83] thereby helping cognitive brain performance. Leptin and cholesterol, whose levels are elevated in metabolic syndrome, also enhance cognitive brain functions [84–87]. Sex and aggression are positively associated in a wide variety of species [88–90], a number of sex hormones also serve as aggression hormones and have a protective role in metabolic disorders [61–65]. Serotonin suppresses sexual desire [91,92] which is also compatible with the hypothesis.

Aggressive behaviour facilitates the secretion of epidermal growth factor (EGF) in saliva and other body fluids [93–95]. This could be in anticipation of wounds during fights since the main role of EGF is in wound healing. Since animals lick wounds, saliva is the most appropriate fluid to secrete EGF. The plasma levels of EGF are shown to be important in pancreatic beta cell regeneration as well [96,97]. Loss of aggression therefore can affect beta cell function through EGF deficiency. It is interesting to note that a number of studies show an association between beta cell damage and histological changes in salivary glands [98–100] although these studies neither estimate EGF nor indicate the direction of the arrow of causation.

## Evaluation of the hypothesis

### *The meta-analysis approach*

If metabolic syndrome is primarily related to aggression control, the signalling molecules associated with aggression control could also be involved in inducing insulin resistance and associated physiological changes. We searched literature for all known endocrine mechanisms contributing to physical aggression or its control. Then we searched for the association of these mechanisms with any components of IRS. A wide variety of molecules were found to be associated with both aggression regulation and metabolic syndrome. These molecules and their association with aggression and with obesity, insulin resistance, cholesterol levels and systemic inflammation are summarized in Table 1 and each molecule is discussed individually below.

It can be seen from Table 1 that a large number of signal molecules that are involved in aggression regulation are also involved in some way or the other with metabolic syndrome. However, it can be argued that since both aggressive behaviour and components of metabolic syndrome are affected by a large number of factors, it is possible to get many molecules that have an action on both by chance alone. We therefore look carefully at the direction of action

**Table 1**
Molecules that affect aggressive behaviour as well as obesity and metabolic syndrome.

| Signalling molecules | Physical aggression | IR | Insulin secretion/ pancreatic regeneration | Oxidative stress | Obesity | Sexual and reproductive function | Inflammation | Angiogenesis |
|---|---|---|---|---|---|---|---|---|
| Brain serotonin | ↓A2, B | ↑A, B | ↑↓A2 | | ↓A1, ↑A2 (TD) | ↓A2 | ↑A2 | |
| Dopamine | ↑A2,B | ↓C | | | ↓C | ↑B | | |
| Melatonin | ↑A2 | ↓A2 | ↓A2 | ↓A2 | ↓A2 | ↑↓(DD) | ↓A2 | |
| Epinephrine | ↑A | ↑A2, ↓C | | | ↓C | | ↑A2 | |
| Norepinephrine | ↑↓DD | ↑C | | | ↑C | | | |
| eNOS | ↑A1 | ↓A1 | | | | | ↑↓A2 | ↑A1 |
| nNOS | ↑↓A1 | ↑A1 | | | | | | |
| Sildenafil | ↑A2 | ↓A2 | | | | ↑A2 | | |
| Testosterone | ↑A2 | ↓A2 | | ↓A2 | ↓C,A2 | ↑A2 | ↓A2 | ↑A2 |
| Estradiol | ↑A2 | ↓A2 | | ↓A2 | ↑C | ↑A2 | ↑↓A2 | ↑A2 |
| DHEA | ↑C | ↓A2 | | | ↓A2 | | ↓A2 | ↑↓(DD) |
| Glucocorticoids | ↓C | ↑A2 | | | ↑C | ↑↓A2 (TD) | | |
| Cholesterol | ↓A2 | ↑C | | | ↑C | | | |
| Leptin | ↓C | ↑C | | | ↓A1, ↑C | | | ↑A1 |
| EGF | ↑B | | ↑A2 | ↓A2 | | | | |
| CB1 | ↓A1 | | | | ↑A1 | | | |
| Endorphins | ↓C | ↓A, ↑C | ↑A2 | | ↑C | ↓A2 | | |
| Plasma glucose | ↓A2 | ↑B | | | | | | |
| Adiposity | ↓C | ↑A2 | | | | | ↑A2 | |
| Triglycerides | ↓A2 | ↑C | | | | | | |
| IGF-1 | ↑C | ↓A1 | | | ↑C, ↓A2 | | | |
| Growth hormone | ↑A2 | ↑A2 | | | ↓C | | | |
| Substance P | ↑↓A1 | | ↑↓A1, DD | | ↑A2 | | | ↑A2 |
| Cholecystokinin | ↑A1, B | ↓C | ↑A2 | | ↓A2 | | | |
| Gastrin | ↑A1 | ↓A1 | | | ↓A1 | | | |
| Ghrelin | ↑C | ↓C | | | ↓C | | | |
| ACTH | ↓A2 | ↑A2 | | | ↓A2 | | ↑A2 | |
| Melanocortin | ↑A1 | ↓A2 | | | ↓A1 | | | |
| Vasopressin | ↑C | ↑C | | | | | ↓A2 | |
| Myostatin | ↓A1 | ↑A1 | | | ↑A1 | | | |
| Osteocalcin | ↑C | ↓A2 | | | ↓A2 | | | |
| Vitamin D | ↑A1 | ↓A2 | | | | | | |

The arrows indicate up regulation or positive correlation and down-regulation or negative correlation. The nature of evidence is indicated as follows: A1 = a mutant or knock-out experiment; A2 = a pharmacological/physiological experiment based on infusion or use of agonists/antagonists. Both A1 and A2 indicate the molecule has a causative role. B indicates a reverse causation i.e. aggression/insulin resistance alters the parameter whereas C indicates only statistical association without a direct evidence for causality. DD = dose dependent and TD = time course dependent action.
See text for references. In cases where a large volume of literature is available, such as for the association of low cholesterol with aggression, only a few reviews or key papers are cited.

to test whether these associations are non-random. The analysis suffers from some deficiencies in data. For example eNOS and nNOS have different effects on aggressive behaviour but the effects of iNOS haven't been studied. Therefore currently there are many gaps in the table. Another potential limitation of this analysis is that the action of each of the molecules cannot be said to be completely independent of others. There are many cross connections between different signalling pathways. We attempted to avoid obvious duplications by not listing more than one molecules of a signalling pathway. For example a hormone, its receptor and the enzymes making or degrading either of them were not listed separately. However, where two molecules had some synergistic action but also had some non-overlapping action, they were listed separately. Some molecules have complex dual actions dependent on dose or time course. In such cases both the actions were separately considered for the quantitative analysis.

We were able to find 32 factors that affect physical aggression as well as insulin resistance. Among these factors there is a highly significant negative association between aggression and insulin resistance parameters, i.e. most pro-aggression factors are insulin sensitizing and anti-aggression factors induce insulin resistance (Chi square = 14.28, $p = 0.0002$). A negative association between pro-aggression factors and obesity (Chi square = 6.89, $p = 0.009$) is also in strong support to our hypothesis.

*Signals that affect physical aggression as well as insulin resistance*

1. *Brain serotonin:* The role of serotonin in aggression control is well known across vertebrate taxa [102–110]. Dominant individuals have low serotonin as compared to subordinate ones in animal societies [66–70] and elevation of serotonin activity in a dominant individual changes its behaviour to that of a subordinate [66]. The arrow of causation appears to be dual, i.e. change in serotonin levels affects aggression and aggressive behaviour modulates serotonin levels [106–107]. In humans low serotonin activity is associated with impulsive aggression or violent suicide [68,110,111]. In agreement with our hypothesis, chronically elevated levels of this anti-aggression molecule in the ventromedial hypothalamus induce insulin resistance [82,83,112]. Reciprocally hyperinsulinemia and insulin resistance results in elevated serotonin levels [113]. Serotonin plays a positive role in memory and cognitive functions [76,78–80,114] and reduces bone mass and strength [115]. Serotonin has a pro-inflammatory effect [116] and it decreases sexual motivation [91,92]. All these changes are coherent with the aggression suppressed subordinate status. Serotonin therefore appears to be a key molecule bridging metabolic syndrome and aggression control. However, the relationship of serotonin with obesity is complex. Serotonin is a satiety hormone and should work as an anti-obesity factor since it regulates food intake. Serotonin receptor knockouts are obese as expected [117]. Selective serotonin reuptake inhibitors that increase the extracellular serotonin levels have been proposed to be effective anti-obesity drugs but paradoxically many of them lead to weight gain and insulin resistance in the long run [118,119]. It is possible that although elevated serotonin may arrest obesity in the short run, a chronic elevation may lead to "serotonin resistance" [120] that eventually leads to obesity and insulin resistance.
2. *Dopamine:* Dopamine activity is positively associated with aggression and the arrow of causation can be dual [106,111,121]. In contrast to serotonin, dopamine produces cognitive deficits [122] but facilitates physical strength. The deletion of DAT gene (dopamine transporter) results in osteopenia and deficiencies in skeletal structure and integrity [123] illustrating the role of dopamine in physical strength. Dopamine has facilitative effect on sexual motivation [124]. In mice, the use of dopamine receptor antagonist is associated with weight gain and insulin resistance whereas agonists of the D1 and D2 dopamine receptor isoforms decrease food intake and improve insulin sensitivity [125]. The observation that diabetes is associated with decreased dopamine activity [126] is consistent with our hypothesis.
3. *Melatonin:* Exposure to short days or short day-like patterns of melatonin increases aggression. Subcutaneous injections of melatonin also increase aggression in male Syrian hamsters [127]. Administration of this pro-aggression hormone has been shown to reduce hyperinsulinemia, hypertriglyceridemia and hyperleptinemia [128,129]. Melatonin acts as a regulator of obesity [129], an anti-inflammatory signal [130] as well as a scavenger of free radicals helping to reduce oxidative stress [131]. Melatonin shows dose dependent effect on sexual activity being a stimulant in small doses and an inhibitor in large repeated doses [132]. The pro-aggression hormone melatonin and the aggression suppression hormone serotonin have opposite effects on insulin secretion from pancreatic islets. Melatonin reduced insulin response to specific and non-specific stimuli whereas serotonin significantly enhanced both specific and non-specific stimulated insulin release except at very high concentrations of glucose [133,134].
4. *Epinephrine:* Overexpression of PNMT, an enzyme that catalyzes formation of epinephrine from norepinephrine, causes significant increase in aggression [135]. However the effect of epinephrine on insulin resistance is contradictory. On the one hand obesity and insulin resistance are associated with elevated norepinephrine, and reduced epinephrine in urine [136] consistent with our hypothesis. But contrary to it, epinephrine induced insulin resistance [137] and had pro-inflammatory action [138] in some studies.
5. *Norepinephrine:* Norepinephrine has dual [139,140] and dose dependent effects on aggression. Slight activation of central noradrenergic system stimulates aggression while strong activation decreases it [141]. In diabetes there is substantial increase in brain norepinephrine metabolism [142–144] which may be responsible for the reduced aggression in diabetes.
6. *Nitric oxide synthase (NOS):* The three isoforms of NOS namely endothelial (eNOS), neuronal (nNOS) and inducible (iNOS) have complex effects on aggressive behaviour as well as on metabolic syndrome. Male mice with targeted deletion of eNOS gene display dramatic reduction in aggression [145]. eNOS knock-out mice were hypertensive and had fasting hyperinsulinemia, hyperlipidemia and insulin resistance [146]. eNOS gene polymorphisms have a significant association with type 2 diabetes [147]. eNOS also has a significant role in facilitating wound repair and growth-factor stimulated angiogenesis [148,149]. Based on different model systems and different cell types/tissues examined, eNOS has both pro-inflammatory and anti-inflammatory effects [150] but it has a protective role against pancreatitis [151]. The effects of nNOS on aggression are sex specific in mice. In males nNOS knock-out mice showed large increase in aggressive behaviour and excess sexual behaviour [152]. Inhibitors of nNOS also increase aggression in males [153,154]. Female nNOS knock outs do not show increased aggression and may in fact show a decrease [155]. As opposed to eNOS knockouts which develop insulin resistance in both liver and peripheral tissue, nNOS knockouts

develop only latter [156]. It is apparent therefore that eNOS which has clearly a pro-aggression action is anti-diabetic and nNOS that has a mixed action on aggression, also has mixed effects on insulin resistance. The inducible form iNOS has not been studied from the behavioural point of view but targeted disruption of iNOS synthase protects against obesity induced IR [157]. The role of NOS in sexual function is well known and sildenafil, a popular drug used for the treatment of erectile dysfunction has insulin sensitizing effects [158] but aggressive behaviour is a possible side effect [159,160].

7. *Sex hormones:* Both testosterone and estradiol promote aggression [161–163]. Dominant males have higher testosterone levels than subordinate ones [71]. Obesity and metabolic syndrome, on the other hand, are associated with lower testosterone levels [63,164]. Testosterone facilitates glucose transport in muscles [165], reduces oxidative stress and accompanying cell damage [166,167] and stimulates angiogenesis and vascular regrowth [168]. Estradiol is also shown to promote growth and angiogenesis [169]. Estrogens especially 17 beta-estradiol and estriol are naturally occurring antioxidants themselves [170]. Owing to their multiple actions the sex and aggression hormones have protective effects against metabolic syndrome. In an apparent contradiction increased serum levels of estradiol have been found in obese men as well as in women [171,172] but these studies give only statistical associations without a clear indication of causation.
8. *DHEA:* DHEA is an adrenal androgen precursor and is important for expression of animal aggression in non-breeding season when gonadal testosterone synthesis is low [173]. DHEA administration protects against fat accumulation and development of muscle insulin resistance in rats [174–176]. DHEA also has anti-inflammatory properties [177]. Effect of DHEA on angiogenesis is contradictory and dose dependent [178]. Although at higher concentrations DHEA inhibited in vitro endothelial cell proliferation, at concentration found in blood it enhanced vascular endothelial proliferation [179]. Exogenous application of DHEA accelerated wound healing [180].
9. *Glucocorticoids:* Low basal levels of glucocorticoids are associated with increased aggression [173,181]. Children with aggressive antisocial behaviour have lower resting levels of cortisol [173]. Adult mice with low baseline levels of corticosterone are more likely to become dominant [173]. Upon aggressive interactions glucocorticoids increase both in dominant and subordinate individuals but in dominant individuals the levels come down more quickly than in subordinate ones [182]. Chronically elevated corticoids result in lowering aggression as well as impairing sex and reproduction whereas short term rise may show an opposite effect on both [183]. Consistent with our hypothesis glucocorticoids contribute to insulin resistance [184–186] and osteoporosis [187].
10. *Cholesterol:* Hypercholesterolemia is an important component of metabolic syndrome which has a strong negative association with physical aggression [22,23,188,189]. Cholesterol lowering drugs induce aggression indicating that cholesterol may be actively involved in aggression control [188]. Monkeys fed with low fat, low cholesterol diet exhibited more aggression than monkeys fed with high fat, high cholesterol diet [23]. As opposed to physical aggression verbal aggression is either not correlated or positively correlated to cholesterol [189]. This is compatible with our assumption that verbal aggression is a 'diplomat' rather than a 'soldier' trait.
11. *Leptin:* Although leptin regulates hyperphagia and obesity, the plasma levels of leptin go up in obesity [171] and this is believed to be accompanied by leptin resistance [190]. Increased leptin levels are frequently associated with increased insulin levels [190] and similar to insulin, leptin is shown to enhance cognitive functions [86]. Leptin levels are negatively associated with aggression [22,23]. Leptin also increases angiogenesis [191] and leptin resistance may interfere with it.
12. *Epidermal growth factor (EGF):* Following physical aggression submandibular salivary glands release EGF [93,95] presumably in anticipation of injuries. EGF not only enhances wound healing but also has a stimulatory effect on beta cell replication [97]. Brand et al. [96] showed that physiologically significant improvement in glucose tolerance could be achieved through stimulating beta cell regeneration with EGF administration. EGF also has a neuroprotective effect through inhibition of free radical neurotoxicity and lipid peroxidation [192].
13. *CB1:* Physiological actions of endocannabinoids in the CNS are mediated by activation of a specific cannabinoid receptor, the CB1 receptor. CB1 has a role in fat accumulation and CB1 blockade has been used for treatment of obesity [193]. CB1 knock-out mice show increased aggression [194] demonstrating a negative association between obesity and aggression. But contrary to expectation CB1 knockouts showed improved learning and memory processes [194].
14. *Endorphin:* Endorphin levels are negatively correlated with aggression scores in rodents and raised endorphin in submissive individuals was accompanied by raised plasma glucose [195]. Endorphins were shown to have inhibitory effects on aggression and reproductive behaviours in birds [196]. Observation of raised plasma levels of endorphin in obese children and adults is consistent with our hypothesis [197,198]. Beta endorphin is also associated with overeating and obesity in mice and rats [199] as well as humans [198,199]. Thus endorphin also links aggression and obesity negatively. In contradiction, role of endorphins in exercise-induced improvement in insulin resistance is shown [200].
15. *Plasma glucose and insulin:* It is likely that hyperinsulinemia and insulin resistance itself is involved in aggression control. Parameters of insulin sensitivity were shown to be positively correlated to violent suicide [201], an association similar to low cholesterol. Low levels of plasma glucose are long known to stimulate aggression [202–204]. Anthropologists have consistently reported a correlation between hypoglycemia and aggressive behaviour across different ethnic groups although whether there is a causal link is debated [205].
16. *Fat and triglycerides:* Plasma triglyceride levels which are positively associated with insulin resistance [206] are negatively correlated with aggression [207] consistent with the hypothesis.
17. *IGF-1:* A significant positive association has been shown between IGF-1 mRNA expression and level of aggression in fish [208]. Dominant pudu males had higher IGF-1 levels than their subordinate pen mates [209]. Although statistically IGF-1 is positively associated with obesity [210], IGF-1 treatment reduced hyperphagia, obesity, hyperinsulinemia and hyperleptinemia in rats [211]. Liver IGF-1 deficient mice showed muscle insulin resistance [212]. Therefore IGF-1 has pro-aggression and anti-insulin-resistance action supporting the hypothesis.
18. *Growth hormone:* GH administration increased isolation-induced aggression [37,213] on the other hand GH secretion is blunted profoundly in individuals with obesity [214].

Growth hormone deficiency in adults is characterized by central obesity. However, contrary to expectation GH induced insulin resistance in some studies [215,216].

19. *Substance P:* The peptide neurotransmitter substance P is certainly involved in regulation of aggression but appears to have a complex role. On the one hand it is vital for territorial as well as defensive aggression [217,218] but on the other its effects via NK1 regulates aggression [219]. Substance P antagonist prevented weight gain and fat accumulation in mice [220]. Substance P has a stimulative effect on glucose-induced insulin secretion from isolated rat islets under normobaric oxygen condition of incubation and it depressed insulin secretion under high baric oxygen incubation [221]. Substance P stimulated angiogenesis within the rat knee synovium [222]. Substance P certainly plays a role in both aggression and metabolic syndrome but its actions on both appear to be complex.
20. *Cholecystokinin (CCK):* Higher expressions of CCK and CCK2R were associated with aggression in transgenic mice overexpressing progastrin [223]. In normal mice brain CCK levels elevated following aggressive encounters in adults or rough and tumble play in adolescents [224]. Following the expectations of the hypothesis CCK has anti-obesity and anti-diabetic effects. Lack of CCK-A receptors in OLETF rats resulted in a satiety deficit, leading to hyperphagia and obesity and after exogenous peripheral administration, CCK reduced food intake [225]. CCK-8 exerts an antidiabetogenic action [226]. CCK is known to induce growth of exocrine pancreas and to stimulate insulin secretion [227]. CCK-B/gastrin receptors also enhance wound healing [228]. It is likely therefore that this pro-aggression molecule may prove to be a key link to reversal of metabolic syndrome.
21. *Gastrin:* A significant increase in the aggression, locomotor activity, and anxiety-like behaviours was detected in the transgenic mice overexpressing progastrin [223]. On the other hand abdominal obesity and insulin resistance were increased in mutant mice lacking gastrin gene expression [229] demonstrating that gastrin is also a pro-aggression anti-obesity and anti-diabetic factor.
22. *Ghrelin:* Ghrelin levels are negatively associated with cholesterol and violent individuals have low cholesterol and leptin along with elevated ghrelin [230]. Although ghrelin is known to enhance appetite [231,232] and thereby expected to increase obesity, low plasma ghrelin levels are associated with type 2 diabetes, insulin resistance and hypertension [233,234]. The low ghrelin levels may be one of the factors responsible for lowered aggressiveness of diabetic patients.
23. *ACTH:* It was found that whilst adrenalectomy reduced aggression, ACTH injection reversed it indicating a pro-aggression role of ACTH [235]. However, contrary to the expectation of the hypothesis, ACTH was observed to promote an insulin-resistant, pro-inflammatory state [236].
24. *Melanocortin:* In rodents melanocortin is shown to promote intermale aggression [237] and peripheral administration of melanotan II, an agonist of melanocortin, increases insulin sensitivity and improves glucose tolerance, an action compatible with the hypothesis [238].
25. *Vasopressin:* Vasopressin enhances aggression [239] but contrary to our expectation it is elevated in diabetes [240].
26. *Bone and muscle strengthening factors:* Strength of muscle and bones is essential for successful physical aggression. Therefore it would be logical to expect that many bone and muscle strengthening factors have pro-aggression and anti-diabetic action. Disruption of the vitamin D receptor gene results in loss of aggression in mice [241] accompanied by increase in grooming behaviour [242]. As per the prediction of the hypothesis Vitamin D deficiency is identified as a significant contributor to insulin resistance [243] and Vitamin D3 supplementation is shown to be an effective insulin sensitizer [244]. A marker of bone formation and strength, osteocalcin induces beta cells to release insulin and also induces the release of adiponectin [245]. Myostatin which sets the limit to muscle growth [246] increases insulin resistance [247] and myostatin inhibitors prevent the development of obesity and type 2 diabetes [248].

### *Volunteer trials for behavioural intervention*

If lack of cues for aggressive behaviour predisposes to metabolic syndrome, it is likely that physical and mental activities mimicking some of the cues may be able to partially reverse the condition. As a preliminary test of this concept we designed a series of physical exercises, activities and games (Watve, patent pending) that involve neuro-motor actions characteristic of Stone Age hunting or combat. A group of 19 type 2 diabetic patient volunteers that had a history of diabetes for at least one year and had HbA1c levels consistently above 7% were given training in these exercises in a 4 day residential camp. The exercise schedule during the camp was accompanied by isolation of the patients for about an hour a day in a place away from human habitation. No change in their current diet and medication was advocated throughout the study. The participants were then asked to continue some of these exercises accompanied by self monitoring for the next three months. Fasting blood samples were collected prior to and after the camp as well as at 1 and 3 month follow up. The self reported compliance with the exercises after the camp varied from 15% to 75%. The study was not intended to be a randomized controlled trial, but only a pilot scale volunteer trial and since this paper is mainly intended to present a hypothesis we only give an outline of the results.

1. *Glycemic control:* As compared to pre-camp levels there was a significant decrease in mean HbA1c in 1 month (paired $t = 2.97$, $p = 0.008$) which continued to decline till 3 months (paired $t = 4.86$, $p = 0.0001$) (Fig. 1).
2. *Inflammatory markers:* As a marker of systemic inflammation we monitored the plasma C reactive protein (CRP) levels of all the above samples. There was a significant decrease (1193 ng/ml) in mean CRP between the pre-camp and post camp samples (paired $t = 1.72$, $p$ one-tailed = 0.05) and the 1st and 3rd month follow up samples did not differ significantly from the post camp samples although a weak declining trend continued (Fig. 1b).

There was no significant reduction in mean body weight during the study period indicating that change in energy balance may not account for the observed differences. The small sample size and preliminary nature of the trial does not allow one to make confident inferences but it certainly raises the likelihood that a behavioural intervention may have a promise in reversal of the metabolic and immune changes and warrants further studies with carefully designed randomized control trials.

### *Consequences of the hypothesis*

The hypothesis allows a reinterpretation of all the signalling pathways and metabolic changes associated with the metabolic syndrome. The reinterpretation is likely to bring us closer to the root cause behind the multiplicity of changes. The current therapies for all the pathological components of metabolic syndrome and type 2 diabetes in particular are aimed only at keeping parameters like blood sugar in control. A "cure" or "reversal" of these conditions is not considered to be their goal. This may be because

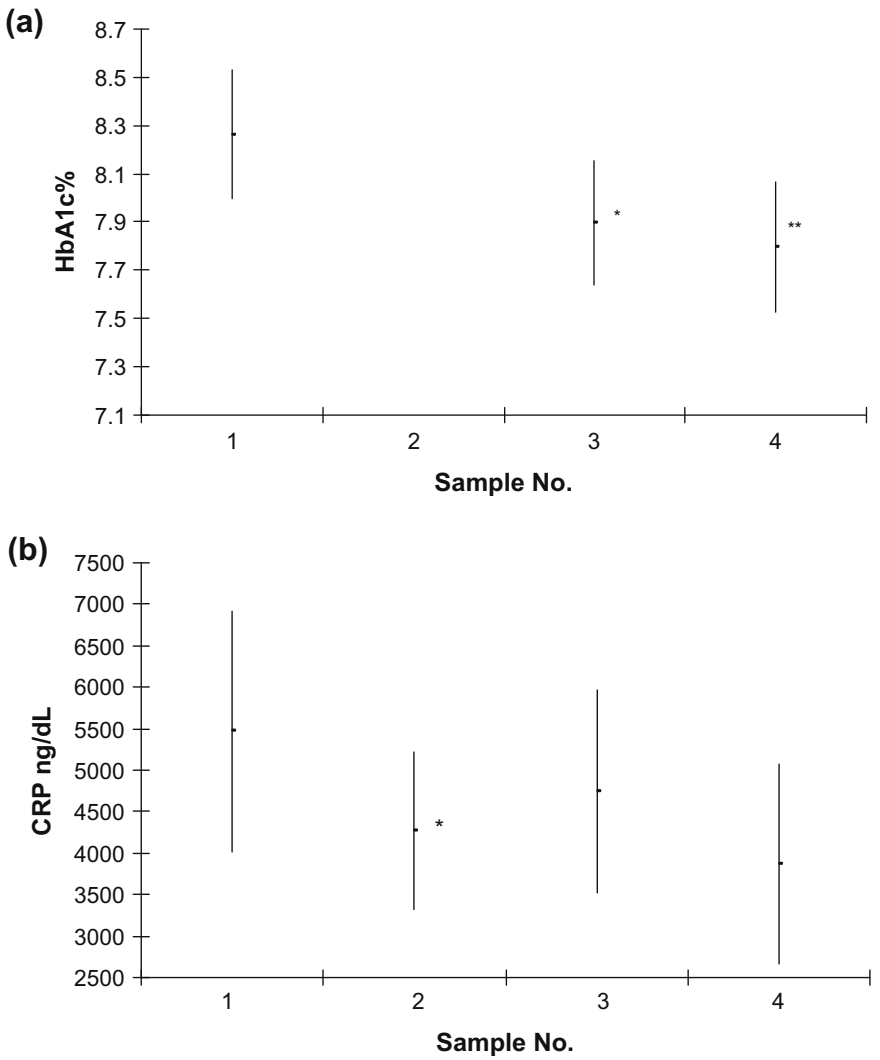


**Fig. 1.** Response of: (a) HbA1c and (b) CRP to behavioural intervention: Mean and standard errors are indicated at $n = 19$. $*$ = Significantly different from pre-treatment levels by paired $t$ test. Double asterisk indicate a highly significant difference. Sample 1: pre-treatment, Sample 2: post camp, Sample 3: 1 month follow up, Sample 4: 3 month follow up.

of our inability to recognize and attack the root cause of metabolic syndrome. A good insight into the root cause is likely to make these conditions reversible and perhaps even curable in future and our hypothesis is a significant step towards it. The central role of the central nervous system in obesity and type 2 diabetes is increasingly recognized [249] and behaviour may hold the key to effective treatment. This raises the possibility of an effective behavioural therapy. Since the preliminary results of behavioural therapy are encouraging, it warrants serious studies with carefully designed clinical trials. Apart from the possibility of effective behavioural therapy, the hypothesis may also lead to identification of novel targets for drug discovery.

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## Conflicts of Interest Statement

None declared.

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## References

[1] Neel JV. Diabetes mellitus: a thrifty genotype rendered detrimental by progress? Am J Human Genet 1962;14:353–62.
[2] Hales CN, Barker DJP. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia 1992;35:595–601.
[3] Stoger R. The thrifty epigenotype: an acquired and heritable predisposition for obesity and diabetes. Bioessays 2008;30(2):156–66.
[4] Speakman JR. Thrifty genes for obesity and the metabolic syndrome-time to call off the search? Diab Vasc Dis Res 2006;3:7–11.
[5] Speakman JR. A non-adaptive scenario explaining the genetic predisposition to obesity: the "predation release" hypothesis. Cell Metab 2007;6:5–12.
[6] Watve MG, Yajnik CS. The evolutionary origins of insulin resistance: a behavioral switch hypothesis. BMC Evolut Biol 2007;7:61. doi:10.1186/1471-2148-7-61.
[7] Moalem S, Strey KB, Percy ME, Peros MC, Perl DP. The sweet thing about type I diabetes: a cryoprotective evolutionary adaptation. Med Hypotheses 2005;65:8–16.

[8] Rashidi A, Kirkwood TBL, Shanley DP. Metabolic evolution suggests an explanation for the weakness of antioxidant defences in beta-cells. Mechan Ageing Develop 2009;130:216–21.
[9] Watve MG, Mandani S. Why serum chemokine levels are raised in insulin resistance syndrome: an immune reversal hypothesis. Curr Sci 2008;95(2):171–4.
[10] Belsare P. Reconciliation of thriftiness and behavioral switch, <www.biomedcentral.com/1471-2148/7/61>; 2007.
[11] Ohsawa H, Inoue M, Takenaka O. Mating strategy and reproductive success of male Patas Monkeys (*Erythrocebus patas*). Primates 1993;34(4): 533–44.
[12] Rasmussen J. The influence of horn and body size on the reproductive behavior of the horned rainbow scarab beetle *Phanaeus difformis* (Coleoptera: Scarabaeidae). J Insect Behav 1994;7(1):67–82.
[13] Pilastro A, Bisazza A. Insemination efficiency of two alternative male mating tactics in the guppy (*Poecilia reticulate*). Proc R Soc Lond B 1999;266:1887–91.
[14] Alberts S, Buchan J, Altmann J. Sexual selection in wild baboons: from mating opportunities to paternity success. Animal Behav 2006;72:1177–96. doi:10.1016/j.anbehav.2006.05.001.
[15] Maynard S. Evolution and the theory of games. Cambridge University Press; 1982.
[16] Beckerman S, Erickson PI, Yost J, et al. Life histories, blood revenge, and reproductive success among the Waorani of Ecuador. PNAS 2009;106(20):8134–9.
[17] Sinervo B, Lively C. The rock–paper–scissor game and evolution of alternative male strategies. Nature 1996;380:240–3. doi:10.1038/380240a0.
[18] Benus RF, Bohus B, Koolhaas JM, van Oortmerssen GA. Heritable variation for aggression as a reflection of individual coping strategies. Cellular Mol Life Sci 1991;47(10):1008–19.
[19] Moles A, Bartolomucci A, Garbugino L, et al. Psychosocial stress affects energy balance in mice. Modulation by social status. Psychoneuroendocrinology 2006;31(5):623–33.
[20] Leedom LJ, Meehan WP. The psychoneuroendocrinology of diabetes mellitus in rodents. Psychoneuroendocrinology 1989;14(4):275–94.
[21] Agardh E, Ahlbom A, Andersson T, et al. Work stress and low sense of coherence is associated with type 2 diabetes in middle-aged Swedish women. Diab Care 2003;26(3):719–24.
[22] Golomb BA. Cholesterol and violence: is there a connection? Ann Internal Med 1998;128(6):478–87.
[23] Kaplan JR, Manuck SB, Shively C. The effects of fat and cholesterol on social behavior in monkeys. Psychosomat Med 1991;53(6):634–42.
[24] Perini C, Müller FB, Bühler FR. Suppressed aggression accelerates early development of essential hypertension. J Hypertens 1991;9(6):499–503.
[25] Perini C, Müller FB, Bühler FR. Suppressed aggression and hyperdynamic cardiovascular regulation in normotensive offspring of essential hypertensive parents. J Cardiovasc Pharmacol 1988;12(Suppl 3):S130–3.
[26] Perini C, Müller FB, Rauchfleisch U, Battegay R, Bühler FR. Hyperadrenergic borderline hypertension is characterized by suppressed aggression. J Cardiovasc Pharmacol 1986;8(Suppl 5):S53–6.
[27] Mankar M, Joshi R, Belsare P, Jog M, Watve M. Obesity as a perceived social signal. PLoS One 2008;3(9):e3187;
Adams CF, Liley NR, Gorzalka BB. PCPA increases aggression in male firemouth cichlids. Pharmacology 1996;53(5):328–30. doi:10.1159/000139446.
[28] Hermanides J, Belqhazi L, Michels RP, Hoekstra JB. Lower incidence of type 2 diabetes mellitus with changes in lifestyle: clues from World War II. Ned Tijdschr Geneeskd 2008;152(44):2415–7.
[29] Westlund K. Incidence of diabetes mellitus in Oslo, Norway 1925 to 1954. Report No. 11 of the Life Insurance Companies' institute for medical statistics at the Oslo city hospitals. Brit J Prev Soc Med 1966;20:105–16.
[30] Kulenovic I, Bebertson A, Grujic M, Suljevic E, Smajkic A. The impact of war on Sarajevans with non-insulin-dependent diabetes mellitus. Eur J Public Health 1996;6(4):252–6.
[31] Lorrain DS, Riolo JV, Matuszewich L, Hull EM. Lateral hypothalamic serotonin inhibits nucleus accumbens dopamine: implications for sexual satiety. J Neurosci 1999;19(17):7648–52.
[32] Lorrain DS, Matuszewich L, Friedman RD, Hull EM. Extracellular serotonin in the lateral hypothalamic area is increased during the postejaculatory interval and impairs copulation in male rats. J Neurosci 1997;17(23):9361–6.
[33] Harding CF, Leshner AI. The effects of adrenalectomy on the aggressiveness of differently housed mice. Physiol Behav 1972;8(3):437–40.
[34] van Wolkenten ML, Davis JM, Gong ML, de Waal FBM. Coping with acute crowding by *Cebus paella*. Int J Primatol 2006;27(5):1241–56.
[35] Judge PG, DeWall FBM. Rhesus monkey behaviour under diverse population densities: coping with long-term crowding. Animal Behav 1997;54(3): 643–62.
[36] Matte AC. Effect of isolation-induced aggression in mice on serum creatine kinase. Psychopharmacology 1975;42(2):209–10.
[37] Matte AC. Growth hormone and isolation-induced aggression in wild male mice. Pharmacol Biochem Behav 1981;14(Suppl 1):85–7.
[38] Wongwitdecha N, Marsden CA. Social isolation increases aggressive behaviour and alters the effects of diazepam in the rat social interaction test. Behav Brain Res 1996;75(1–2):27–32.
[39] Sánchez C, Arnt J, Hyttel J, Moltzen EK. The role of serotonergic mechanisms in inhibition of isolation-induced aggression in male mice. Psychopharmacology 1993;110(1–2):53–9.
[40] Sandnabba NK. Selective breeding for isolation-induced intermale aggression in mice: associated responses and environmental influences. Behav Genet 1996;26(5):277–88.
[41] Riste L, Khan F, Cruickshank K. High prevalence of type 2 diabetes in all ethnic groups including Europeans in a British innercity. Diab Care 2001;24:1377–83.
[42] Ellaway A, Macintyre S, Bonnefoy X. Graffiti, greenery and obesity in adults: secondary analysis of European cross sectional survey. Br Med J 2005;331:611–2.
[43] Koch S, Holland RW, Hengstler M, van Knippenberg A. Body locomotion as regulatory process: stepping backward enhances cognitive control. Psychol Sci 2009;20:449–50.
[44] Weisberg S, McCann D, Desai M, Rosenbaum M, Leibel R, Ferrante A. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003;112(12):1796–808.
[45] Kanda H, Tateya S, Tamori Y. MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. J Clin Invest 2006;116(6):1494–505. doi:10.1172/JCI26498.
[46] Madjid M, Awan I, Willerson JT, Casscells SW. Leukocyte count and coronary heart disease: implications for risk assessment. J Am Coll Cardiol 2004;44(10):1945–56.
[47] Maruyama K, Asai J, Li Masaaki, Thorne T, Losordo D, D'Amore P. Decreased macrophage number and activation lead to reduced lymphatic vessel formation and contribute to impaired diabetic wound healing. Am J Pathol 2007;170(4):1178–91.
[48] Thomas M, Tsalamandris C, MacIssac R, Jerums G. Anaemia in diabetes: an emerging complication of microvascular disease. Curr Diab Rev 2005;1(1):107–26.
[49] Schram MT, Chaturvedi N, Schalkwijk CG, Fuller JH, Stehouwer CDA, EURODIAB Prospective Complications Study Group. Markers of inflammation are cross-sectionally associated with microvascular complications and cardiovascular disease in type 1 diabetes – the EURODIAB Prospective Complications Study. Diabetologia 2005;48(2): 370–8.
[50] Saraheimo M, Teppo A-M, Forsblom C, Fagerudd J, Groop P-H, On behalf of the FinnDiane Study Group. Diabetic nephropathy is associated with low-grade inflammation in type 1 diabetic patients. Diabetologia 2003;46(10): 1402–7.
[51] Yan SF, Ramasamy R, Naka Y, Schmidt AM. Glycation, inflammation, and RAGE: a scaffold for the macrovascular complications of diabetes and beyond. Circ Res 2003;93:1159–69.
[52] Zhang L, Zalewski A, Liu Y, et al. Diabetes-induced oxidative stress and low-grade inflammation in porcine coronary arteries. Circulation 2003;108:472–8.
[53] Lopes-Virella MF, Virella G. The role of immune and inflammatory processes in the development of macrovascular disease in diabetes. Front Biosci 2003;8:s750–68.
[54] Zent R, Pozzi A. Angiogenesis in diabetic nephropathy. Semi Nephrop 2007;27(2):161–71.
[55] Yamamoto Y, Maeshima Y, Kitayama H, et al. Tumstatin peptide, an inhibitor of angiogenesis, prevents glomerular hypertrophy in the early stage of diabetic nephropathy. Diabetes 2004;53:1831–40.
[56] Bishop P. Hypoxia, angiogenesis, and proliferative diabetic retinopathy. Endocr Abs 2008;15:S19.
[57] Soher AI, Mostafa MS, Zaki AA. Erythropoietin is a potent ischemia induced angiogenic factor in proliferative diabetic retinopathy. Aust J Basic Appl Sci 2008;2(4):1320–4.
[58] Hayden MR, Tyagi SC. Is type 2 diabetes mellitus a vascular disease (atheroscleropathy) with hyperglycemia a late manifestation? The role of NOS, NO, and redox stress. Cardiovasc Diabetol 2003;2:2.
[59] Lenzen S, Drinkgern J, Tiedge M. Low antioxidant enzyme gene expression in pancreatic islets compared with various other mouse tissues. Free Radic Biol Med 1996;20(3):463–6.
[60] Modak MA, Parab PB, Ghaskadbi SS. Pancreatic islets are very poor in rectifying oxidative DNA damage. Pancreas 2009;38:23Y29.
[61] Kumagai S, Holmang A, Bjorntorp P. The effects of oestrogen and progesterone on insulin sensitivity in female rats. Acta Physiol Scand 1993;149(1):91–7.
[62] Galipeau D, Verma S, Mc-Neill JH. Female rats are protected against fructose-induced changes in metabolism and blood pressure. Am J Physiol Heart Circ Physiol 2002;283:H2478–84.
[63] Holmang A, Bjorntorp P. The effects of testosterone on insulin sensitivity in male rats. Acta Physiol Scand 1992;146(4):505–10.
[64] Muller M, Grobbee DE, den Tonkelaar I, Lamberts SWJ, van der Schouw YT. Endogenous sex hormones and metabolic syndrome in aging men. J Clin Endocrinol Metab 2005;90(5):2618–23.
[65] Andersson B, Mattsson L, Hahn L, et al. Estrogen replacement therapy decreases hyperandrogenicity and improves glucose homeostasis and plasma lipids in postmenopausal women with noninsulin dependent diabetes mellitus. J Clin Endocrinol Metab 1997;82:638–43.
[66] Larson ET, Summers CH. Serotonin reverses dominant social status. Behav Brain Res 2001;121(1–2):95–102.
[67] Semsar K, Perreault HAN, Godwin J. Fluoxetine-treated male wrasses exhibit low AVT expression. Brain Res 2004;1029(2):141–7.
[68] Linnoila VM, Virkkunen M. Aggression, suicidality, and serotonin. J Clin Psychiatry 1992;53(Suppl):46–51.

[69] Higley J, Mehlman P, Taub D, et al. Cerebrospinal fluid monoamine and adrenal correlates of aggression in free-ranging rhesus monkeys. Arch Gen Psychiatry 1992;49(6):436–41.

[70] Higley JD, King Jr ST, Hasert MF, Champoux M, Suomi SJ, Linnoila M. Stability of interindividual differences in serotonin function and its relationship to severe aggression and competent social behaviour in rhesus macaque females. Neuropsychopharmacology 1996;14(1):67–76.

[71] Blanchard DC, Sakai RR, McEwen B, Weiss SM, Blanchard RJ. Subordination stress: behavioral, brain, and neuroendocrine correlates. Behav Brain Res 1993;58(1–2):113–21.

[72] Sapolsky R. Individual differences in cortisol secretory patterns in the wild baboon: role of negative feedback sensitivity. Endocrinology 1983;113(6):2263–7.

[73] Sapolsky RM, Ray JC. Styles of dominance and their endocrine correlates among wild olive baboons (*Papio anubis*). Am J Primatol 1989;18(1):1–13.

[74] Sapolsky RM. Cortisol concentrations and the social significance of rank instability among wild baboons. Psychoneuroendocrinology 1992;17(6):701–9.

[75] Shively C, Kaplan J. Effects of social factors on adrenal weight and related physiology of *Macaca fascicularis*. Physiol Behav 1984;33(5):777–82.

[76] McEntee W, Crook T. Serotonin, memory, and the aging brain. Psychopharmacology 1991;103:143–9.

[77] Clarke H, Dalley J, Crofts H, Robbins T, Roberts A. Cognitive inflexibility after prefrontal serotonin depletion. Science 2004;304:87–880.

[78] Amin Z, Canli T, Epperson C. Effect of estrogen–serotonin interaction on mood and cognition. Behav Cogn Neurosci Rev 2005;4(1):43–58.

[79] Schmitt J, Wingen M, Ramaekers J, Evers E, Riedel W. Serotonin and human cognitive performance. Curr Pharmaceut Des 2006;12(20):2473–86.

[80] Luciana M, Collins P, Depue R. Opposing roles for dopamine and serotonin in the modulation of human spatial working memory functions. Cerebral Cortex 1998;8:218–26.

[81] Kern W, Peters A, Fruehwald-Schultes B, Deininger E, Born J, Fehm HL. Improving influence of insulin on cognitive functions in humans. Neuroendocrinology 2001;74:270–80.

[82] Luo S, Luo J, Cincotta AH. Chronic ventromedial hypothalamic infusion of norepinephrine and serotonin promotes insulin resistance and glucose intolerance. Neuroendocrinology 1999;70(6):460–5.

[83] Rattigan S, Clark M, Barrett E. Acute vasoconstriction – induced insulin resistance in rat muscle in vivo. Diabetes 1999;48:564–9.

[84] Paz-Filho GJ, Babikian T, Asarnow, et al. Leptin replacement improves cognitive development. PLoS ONE 2008;3(8):e3098. doi:10.1371/journal.pone.0003098.

[85] Harvey J, Shanley LJ, O'Malley D, Irving AJ. Leptin: a potential cognitive enhancer? Biochem Soc Trans 2005;33(Pt 5):1029–32.

[86] Farr SA, Banks WA, Morley JE. Effects of leptin on memory processing. Peptides 2006;27(6):1420–5.

[87] Elias PK, Elias MF, D'Agostino RB, Sullivan LM, Wolf PA. Serum cholesterol and cognitive performance in the Framingham heart study. Psychosom Med 2005;67:24–30.

[88] Elias M. Serum cortisol, testosterone, and testosterone-binding globulin responses to competitive fighting in human males. Aggress Behav 1981;7(3):215–24.

[89] Giammanco M, Tabacchi G, Giammanco S, Majo D, La Guardia M. Testosterone and aggressiveness. Med Sci Monit 2005;11(4):RA136–45.

[90] Lamba S, Kazi YC, Deshpande S, Natesh M, Bhadra A, Gadagkar R. A possible novel function of dominance behaviour in queen-less colonies of the primitively eusocial wasp *Ropalidia marginata*. Behav Processes 2007;74:351–6.

[91] Hull EM, Lorrain DS, Du J, et al. Hormone–neurotransmitter interactions in the control of sexual behaviour. Behav Brain Res 1999;105(1):105–16.

[92] Lorrain DS, Riolo JV, Matuszewich L, Hull EM. Lateral hypothalamic serotonin inhibits nucleus accumbens dopamine: implications for sexual satiety. J Neurosci 1999;19(17):7648–52.

[93] Nexo E, Hollenberg MD, Bing J. Aggressive behavior in mice provokes a marked increase in both plasma epidermal growth factor and renin. Acta Physiol Scand 1981;111(3):367–71.

[94] Nexo E, Peter Skov Olsen, Poulsen K. Exocrine and endocrine secretion of renin and epidermal growth factor from the mouse submandibular glands. Regul Pep 1984;8(4):327–34.

[95] Sánchez O, Viladrich M, Ramírez I, Soley M. Liver injury after an aggressive encounter in male mice. Am J Physiol Regul Integr Comp Physio 2007;293:R1908–16.

[96] Brand SJ, Tagerud S, Lambert P, et al. Pharmacological treatment of chronic diabetes by stimulating pancreatic beta-cell regeneration with systemic co-administration of EGF and gastrin. Pharmacol Toxicol 2002;91(6):414–20.

[97] Bouwens L, Rooman I. Regulation of pancreatic beta-cell mass. Physiol Rev 2005;85:1255–70.

[98] Hu Y, Nakagawa Y, Purushotham KR, Humphreys-Beher MG. Functional changes in salivary glands of autoimmune disease-prone NOD mice. Am J Physiol Endocrinol Metab 1992;263:E607–14.

[99] Kamisawa T, Tu Y, Egawa N, Sakaki N, Inokuma S, Kamata N. Salivary gland involvement in chronic pancreatitis of various etiologies. Am J Gastroenterol 2002;98(2):323–6.

[100] Frulloni L, Morana G, Bovo P. Salivary gland involvement in patients with chronic pancreatitis. Pancreas 1999;19(1):33–8.

[102] Clotfelter ED, O'Hare EP, McNitt MM, Carpenter RE, Summers CH. Serotonin decreases aggression via 5-HT1A receptors in the fighting fish *Betta splendens*. Pharmacol Biochem Behav 2007;87(2):222–31 [Epub 2007].

[103] Adams CF, Liley NR, Gorzalka BB. PCPA increases aggression in male firemouth cichlids. Pharmacology 1996;53(5):328–30. doi:10.1159/000139446.

[104] Höglund E, Bakke M, Øverli Ø, Winberg S, Nilsson GE. Suppression of aggressive behaviour in juvenile Atlantic cod (*Gadus morhua*) by L-tryptophan supplementation. Aquaculture 2005;249(1–4):525–31.

[105] Fachinelli C, Sargo S, Bataller R, Rodriguez Echandia EL. Effect of 5-HTP and ketanserine on the aggressive reaction induced by food competition in dominant and submissive pigeons (*Columba livia*). Behav Brain Res 1989;35(3):265–70.

[106] Ferrari PF, van Erp AMM, Tornatzky W, Miczek KA. Accumbal dopamine and serotonin in anticipation of the next aggressive episode in rats. Eur J Neurosci 2003;17:371–8.

[107] Chiavegatto S, Nelson RJ. Interaction of nitric oxide and serotonin in aggressive behavior. Horm Behav 2003;44(3):233–41.

[108] Peremans K, Audenaert K, Hoybergs Y, et al. The effect of citalopram hydrobromide on 5-$HT_{2A}$ receptors in the impulsive–aggressive dog, as measured with $^{123}$I-5-I-R911150 SPECT. Eur J Nucl Med Mol Imag 2005;32(6):708–16.

[109] Westergaard GC, Mehlman PT, Westergaard GC, Suomi SJ, Higley JD. CSF 5-HIAA and aggression in female macaque monkeys: species and interindividual differences. Psychopharmacology 1999;146(4):440–6.

[110] Cleare AJ, Bond AJ. Does central serotonergic function correlate inversely with aggression? A study using D-fenfluramine in healthy subjects. Psychiatry Res 1997;69(2–3):89–95.

[111] Seo D, Patrick CJ, Patrick KJ. Role of serotonin and dopamine system interactions in the neurobiology of impulsive aggression and its comorbidity with other clinical disorders. Aggr Violent Behav 2008;13(5):383–95.

[112] Luo S, Meier AH, Cincotta AH. Bromocriptine reduces obesity, glucose intolerance and extracellular monoamine metabolite levels in ventromedial hypothalamus of Syrian hamsters. Neuroendocrinology 1998;68:1–10.

[113] Singh RB, Pella D, Mechiroea V, Otsuka K. Can brain dysfunction be a predisposing factor for metabolic syndrome? Biomed Pharmacother 2004;58:s56–68.

[114] Richter-Levin G, Segal M. Serotonin, aging and cognitive functions of the hippocampus. Rev Neurosci 1996;7(2):103–13.

[115] Bliziotes M, Gunness M, Eshleman A, Wiren K. The role of dopamine and serotonin in regulating bone mass and strength: studies on dopamine and serotonin transporter null mice. J Musculoskel Neuron Interact 2002;2(3):291–5.

[116] Harbuz MS, Marti O, Lightman SL, Jessop DS. Alteration of central serotonin modifies onset and severity of adjuvant-induced arthritis in the rat. Br J Rheumatol 1998;37:1077–83.

[117] Nonogaki K, Strack AM, Dallman MF, Tecott LH. Leptin-independent hyperphagia and type 2 diabetes in mice with a mutated serotonin 5-HT2C receptor gene. Nat Med 1998;4(10):1152–6.

[118] Raeder MB, Bjelland I, Emil Vollset S, Steen VM. Obesity, dyslipidemia, and diabetes with selective serotonin reuptake inhibitors: the Hordaland Health Study. J Clin Psychiatry 2006;7(12):1974–82.

[119] Harvey BH, Bouwer CD. Neuropharmacology of paradoxic weight gain with selective serotonin reuptake inhibitors. Clin Neuropharmacol 2000;23(2):90–7.

[120] Smolin B, Klein E, Levy Y, Ben-Shachar D. Major depression as a disorder of serotonin resistance: inference from diabetes mellitus type II. Int J Neuropsychopharmacol 2007;10(6):839–50.

[121] van Erp AMM, Miczek KA. Aggressive behaviour, increased accumbal dopamine, and decreased cortical serotonin in rats. J Neurosci 2000;20(24):9320–5.

[122] Cohen JD, Servan S. A theory of dopamine function and its role in cognitive deficits in schizophrenia. Schizophr Bull 1993;19(1):85–104.

[123] Bliziotes M, McLoughlin S, Gunness M, Fumagalli F, Jones SR, Caron MG. Bone histomorphometric and biomechanical abnormalities in mice homozygous for deletion of the dopamine transporter gene. Bone 2000;26(1):15–9.

[124] Hull EM, Muschamp JW, Sato S. Dopamine and serotonin: influences on male sexual behaviour. Physiol Behav 2004;83(2):291–307.

[125] Cincotta AH, Tozo E, Scislowski PWD. Bromocriptine/SKF38393 treatment ameliorates obesity and associated metabolic dysfunctions in obese (ob/ob) mice. Life Sci 1997;61:951.

[126] Murzi E, Contreras Q, Teneus L, et al. Diabetes decreases limbic extracellular dopamine in rats. Neurosci Lett 1996;202(3):141–4.

[127] Jasnow AM, Huhman KL, Bartness TJ, Demas GE. Short days and exogenous melatonin increase aggression of male Syrian hamsters *(Mesocricetus auratus)*. Horm Behav 2002;42:13–20.

[128] Nishida S, Segawa T, Murai I, Nakagawa S. Long term melatonin administration reduces hyperinsulinemia and improves the altered fatty-acid compositions in type 2 diabetes rats via the restoration of △-5 desaturase activity. J Pineal Res 2002;32:26–33.

[129] Marcassus PM, Desbazeille M, Bros A. Melatonin reduces body weight gain in Sprague-Dawley rats with diet induced obesity. Endocrinology 2003. doi:10.1210/en.2003-0693.

[130] Bilici D, Akpinar E, Kiziltunç A. Protective effect of melatonin in carrageenan-induced acute local inflammation. Pharmacol res. 2002;46:133–9.

[131] Nishida S. Metabolic effects of melatonin on oxidative stress and diabetes mellitus. Endocrine 2005;27(2):131–5.
[132] Drago F, Busa L. Acute low doses of melatonin restore full sexual activity in impotent male rats. Brain Res 2000;878:98–104.
[133] Peschke E, Peschke D, Hammer T, Csernus V. Influence of melatonin and serotonin on glucose-stimulated insulin release from perifused rat pancreatic islets in vitro. J Pineal Res 1997;23(3):156–63.
[134] Gagliardino JJ, Nierle C, Pfeiffer EF. The effect of serotonin on in vitro insulin secretion and biosynthesis in mice. Diabetologia 1974;10:411–4.
[135] Sorenson DB, Johnsen PF, Bibby BM, et al. PNMT transgenic mice have an aggressive phenotype. Horm Metab Res 2005;37(3):159–63.
[136] Lee ZS, Critchley JA, Tomlinson B, et al. Urinary epinephrine and norepinephrine interrelations with obesity, insulin, and the metabolic syndrome in Hong Kong Chinese. Metabolism 2001;50(2):135–43.
[137] Deibert DC, DeFronzo RA. Epinephrine-induced insulin resistance in man. J Clin Invest 1980;65:717–21.
[138] Karalis KP, Kontopoulos, Louis E, Muglia J, Majzoub JA. Corticotropin-releasing hormone deficiency unmasks the proinflammatory effect of epinephrine. Proc Natl Acad Sci USA 1999;96:7093–7.
[139] Thoa NB, Eichelman B, Richardson JS, Jacobowitz D. 6-Hydroxydopa depletion of brain norepinephrine and the facilitation of aggressive behaviour. Science 1972;178:75–7.
[140] Volavka J. The neurobiology of violence. J Neuropsychiatry Clin Neurisci 1999;11(3):307–14.
[141] Haller J, Makara GB, Kruk MR. Catecholaminergic involvement in the control of aggression: hormones, the peripheral sympathetic, and central noradrenergic systems. Neurosci Biobehav Rev 1998;22(1):85–97.
[142] Trulson ME, Himmel CD. Effects of insulin and streptozotocin-induced diabetes on brain norepinephrine metabolism in rats. J Neurochem 1985;44(6):1873–6.
[143] Chen CC, Yang JC. Effects of short and long-lasting diabetes mellitus on mouse brain monoamines. Brain Res 1991;552(1):175–9.
[144] Cincotta AH, Luo S, Liang Y. Hyperinsulinemia increases norepinephrine metabolism in the ventromedial hypothalamus of rats. Neuroreport 2000;11(2):383–7.
[145] Demas GE, Kriegsfeld LJ, Blackshaw S. Elimination of aggressive behaviour in male mice lacking endothelial nitric oxide synthase. J Neurosci 1999;19:RC30 (1–5).
[146] Duplain H, Burcelin R, Sartori C, et al. Insulin resistance, hyperlipidemia and hypertension in mice lacking endothelial nitric oxide synthase. Circulation 2001;104:342–5.
[147] Monti LD, Barlassina C, Citterio L, et al. Endothelial nitric oxide synthase polymorphisms are associated with type 2 diabetes and the insulin resistance syndrome. Diabetes 2003;52:1270–5.
[148] Lee P, Salyapongse N, Bragdon G, et al. Impaired wound healing and angiogenesis in eNOS-deficient mice. Am J Physiol Heart Circ Physiol 1999;277:1600–8.
[149] Fukumura D, Gohongi T, Kadambi A, et al. Predominant role of endothelial nitric oxide synthase in vascular endothelial growth factor-induced angiogenesis and vascular permeability. PNAS 2001;98(5):2604–9.
[150] Ying L, Hofseth LJ. An emerging role for endothelial nitric oxide synthase in chronic inflammation and cancer. Cancer Res 2007;67(4):1407–10.
[151] DiMagno MJ, Williams JA, Hao Y, Ernst SA, Owyang C. Endothelial nitric oxide synthase is protective in the initiation of caerulein-induced acute pancreatitis in mice. Am J Physiol Gastrointest Liver Physiol 2004;287:G80–7.
[152] Nelson RJ, Demas GE, Huang PL, et al. Behavioural abnormalities in male mice lacking neuronal nitric oxide synthase. Nature 1995;378(6555):383–6.
[153] Demas GE, Eliasson MJL, Dawson TM, et al. Inhibition of neuronal nitric oxide synthase increases aggressive behavior in mice. Mol Med 1997;3(9):610–6.
[154] Kriegsfeld LJ, Dawson TM, Dawson VL, Nelson RJ, Snyder SH. Aggressive behavior in male mice lacking the gene for neuronal nitric oxide synthase requires testosterone. Brain Res 1997;769(1):66–70.
[155] Gammie SC, Nelson RJ. Maternal aggression is reduced in neuronal nitric oxide synthase-deficient mice. J Neurosci 1999;19(18):8027–35.
[156] Shankar RR, Wu Y, Shen H, Zhu J, Baron AD. Mice with gene disruption of both endothelial and neuronal nitric oxide synthase exhibit insulin resistance. Diabetes 2000;49:1–4.
[157] Perreault M, Marette A. Targeted disruption of inducible nitric oxide synthase protects against obesity-linked insulin resistance in muscle. Nat Med 2001;7:1138–43.
[158] Ayala JE, Bracy DP, Julien BM, Rottman JN, Fueger PT, Wasserman DH. Chronic treatment with sildenafil improves energy balance and insulin action in high fat-fed conscious mice. Diabetes 2007;56:1025–33.
[159] Milman HA, Arnold SB. Neurologic, psychological, and aggressive disturbances with sildenafil. Ann Pharmacother 2002;36(7–8):1129–34.
[160] Hotchkiss AK, Pyter LM, Gatien ML, Wen JC, Milman HA, Nelson RJ. Aggressive behavior increases after termination of chronic sildenafil treatment in mice. Physiol Behav 2005;83(5):683–8.
[161] van Bokhoven I, van Goozen SH, van Engeland H, et al. Salivary testosterone and aggression, delinquency, and social dominance in a population-based longitudinal study of adolescent males. Horm Behav 2006;50(1):118–25.
[162] Michael RP, Zumpe D. A review of hormonal factors influencing the sexual and aggressive behavior of macaques. Am J Primatol 1993;30:213–41.
[163] Albert DJ, Jonik RH, Walsh ML. Hormone-dependent aggression in male and female rats: experiential, hormonal, and neural foundations. Neurosci Biobehav Rev 1992;16(2):177–92.
[164] Stewart T, Baker G. The inverse relationship between obesity and testicular function. Obesity 2008;10(4):34–6.
[165] Tsai LW, Sapolsky RM. Rapid stimulatory effects of testosterone upon myotubule metabolism and sugar transport, as assessed by silicon microphysiometry. Aggr behav 1996;22:357–64.
[166] Ahlbom E, Prins GS, Ceccatelli S. Testosterone protects cerebellar granule cells from oxidative stress-induced cell death through a receptor mediated mechanism. Brain Res 2001;892(2):255–62.
[167] Tunez I, Feijoo M, Collado JA, et al. Effect of testosterone on oxidative stress and cell damage induced by 3-nitropropionic acid in striatum of ovariectomized rats. Life Sci 2007;80(13):1221–7.
[168] Franck-Lissbrant I, Häggström S, Damber Jan-Erik, Bergh A. Testosterone stimulates angiogenesis and vascular regrowth in the ventral prostate in castrated adult rats. Endocrinology 1998;139(2):451–6.
[169] Dabrosin C, Palmer K, Muller WJ, Gauldie J. Estradiol promotes growth and angiogenesis in polyoma middle T transgenic mouse mammary tumor explants. Breast Cancer Res Treatment 2003;78:1–6.
[170] Mooradian AD. Antioxidant properties of steroids. J Steroid Biochem Mol Biol 1993;45(6):509–11.
[171] Klein KO, Larmore KA, de Lancey E, Brown JM, Considine RV, Hassink SG. Effect of obesity on estradiol level, and its relationship to leptin, bone maturation, and bone mineral density in children. J Clin Endocrinol Metab 1998;83(10):3469–75.
[172] Kley HK, Solbach HG, McKinnan JC, Krüskemper HL. Testosterone decrease and oestrogen increase in male patients with obesity. Acta Endocrinol 1979;91(3):553–63.
[173] Soma KK, Scotti M, Newman AEM, Charlier TD, Demas GE. Novel mechanisms for neuroendocrine regulation of aggression. Front Neuroendocrinol 2008;29(4):476–89.
[174] Cleary MP, Zisk JF. Anti-obesity effect of two different levels of dehydroepiandrosterone in lean and obese middle-aged female Zucker rats. Int J Obes 1986;10(3):193–204.
[175] Han DH, Hansen PA, Chen MM, Holloszy JO. DHEA treatment reduces fat accumulation and protects against insulin resistance in male rats. J Gerontol Series A: Biol Sci Med Sci 1998;53(1):B19–24.
[176] Hansen PA, Han DH, Nolte LA, Chen M, Holloszy JO. DHEA protects against visceral obesity and muscle insulin resistance in rats fed a high-fat diet. Am J Physiol Regul Integr Comp Physiol 1997;273:1704–8.
[177] López-Marure R, Huesca-Gómez C, Ibarra-Sánchez Mde J, Zentella A, Pérez-Méndez O. Dehydroepiandrosterone delays LDL oxidation in vitro and attenuates several oxLDL-induced inflammatory responses in endothelial cells. Inflam Allergy Drug Targets 2007;6(3):174–82.
[178] Varet J, Vincent L, Akwa Y, et al. Dose-dependent effect of dehydroepiandrosterone, but not of sulphate ester on angiogenesis. Eur J Pharmacol 2004;502:21–30.
[179] Liu D, Iruthayanathan M, Homan LL, et al. Dehydroepiandrosterone stimulates endothelial proliferation and angiogenesis through extracellular signal-regulated kinase 1/2 mediated mechanisms. Endocrinology 2008;149(3):889–98.
[180] Mills SJ, Ashworth JJ, Gilliver SC, Hardman MJ, Ashcroft GS. The sex steroid precursor DHEA accelerates cutaneous wound healing via the estrogen receptors. J Invest Dermatol 2005;125:1053–62.
[181] Demas GE, Cooper MA, Albers HE, Soma KK. Novel mechanisms underlying neuroendocrine regulation of aggression: a synthesis of rodent, avian, and primate studies. Berlin, Heidelberg: Springer-Verlag; 2007. p. 338–372.
[182] Sapolsky RM. Social status and health in humans and other animals. Annu Rev Anthropol 2004;33:393–418.
[183] Summers CH, Watt MJ, Ling TL, et al. Glucocorticoid interaction with aggression in non-mammalian vertebrates: reciprocal action. Eur J Pharmacol 2005;526(1–3):21–35.
[184] Andrews RC, Walker BR. Glucocorticoids and insulin resistance: old hormones, new targets. Clin Sci 1999;96:513–23.
[185] Macfarlane DP, Forbes S, Walker BR. Glucocorticoids and fatty acid metabolism in humans: fuelling fat redistribution in the metabolic syndrome. J Endocrinol 2008;197:189–204.
[186] Christiansen JJ, Djurhuus CB, Gravholt CH, et al. Effects of cortisol on carbohydrate, lipid, and protein metabolism: studies of acute cortisol withdrawal in adrenocortical failure. J Clin Endocrinol Metab 2007;92(9):3553–9.
[187] Ishida Y, Heersche JNM. Glucocorticoid induced osteoporosis: both in vivo and in vitro concentrations of glucocorticoids higher than physiological levels attenuate osteoblast differentiation. J Bone Mineral Res 1998;13:1822–6.
[188] Golomb BA, Criqui MH, White H, Dimsdale JE. Conceptual Foundations of the UCSD statin study. A randomized controlled trial assessing the impact of statins on cognition, behavior, and biochemistry. Arch Int Med 2004;164:153–62.
[189] Hillbrand M, Spitz RT. Cholesterol and aggression. Aggr Violent Behav 1999;4(3):359–70.
[190] Widjaja A, Stratton IM, Horn R, Holman RR, Turner R, Brabant G. UKPDS 20: plasma leptin, obesity, and plasma insulin in type 2 diabetic subjects. J Clin Endocrinol Metabol 1997;82(2):654–7.
[191] Sierra-Honigmann MR, Nath AK, Murakami C, et al. Biological action of leptin as an angiogenic factor. Science 1998;281(5383):1683–6.
[192] Peng H, Wen TC, Tanaka J, et al. Epidermal growth factor protects neuronal cells *in vivo* and in vitro against transient forebrain ischemia –

and free radical – induced injuries. J Cerebral Blood flow Metab 1998;18:349–60.
[193] Viveros MP, Rodriguez de Fonseca F, Bermudez-Silva FJ, McPartland JM. Critical role of the endocannabinoid system in the regulation of food intake and energy metabolism, with phylogenetic, developmental, and pathophysiological implications. Endocr Metab Immune Disord – Drug Targets 2008;8:220–30.
[194] Martin M, Ledent C, Parmentier M, Maldonado R, Valvorde O. Involvement of CB1 cannabinoid receptors in emotional behaviour. Psychopharmacology 2002;159:379–87.
[195] Tordjman S, Carlier M, Cohen D, et al. Aggression and the three opioid families (endorphins, enkephalins, and dynorphins) in mice. Behav Genet 2003;3(5):529–36.
[196] Kotegawa T, Abe T, Tsutsui K. Inhibitory role of opioid peptides in the regulation of aggressive and sexual behaviors in male Japanese quails. J Exp Zool 1997;277(2):146–54.
[197] Giugliano D, Lefebvre PJ. A role for beta-endorphin in the pathogenesis of human obesity? Horm Metab Res 1991;23(6):251–6.
[198] Giugliano D, Cozzolino D, Salvatore T, et al. Physiological elevations of plasma beta-endorphin alter glucose metabolism in obese, but not normal-weight, subjects. Metabolism 1992;41(2):184–90.
[199] Margules DL, Moisset B, Lewis MJ, Shibuya H, Pert CB. Beta-endorphin is associated with overeating in genetically obese mice (*ob/ob*) and rats (*fa/fa*). Science 1978;202(4371):988–91.
[200] Su CF, Chang YY, Pai HH, Liu IM, Lo CY, Cheng JT. Mediation of beta endorphin in exercise-induced improvement in insulin resistance in obese Zucker rats: focus on cardiovascular disease in diabetes. Diab/Metab Res Rev 2005;21(2):175–82.
[201] Golomb BA, Tenkanen L, Alikoski T, et al. Insulin sensitivity markers: predictors of accidents and suicides in Helsinki Heart Study screenees. J Clin Epidemiol 2002;55(8):767–73.
[202] Andrade ML, Benton D, Brain PF, Ramirez JM, Walmsley SV. A reexamination of the hypoglycemia-aggression hypothesis in laboratory mice. Int J Neurosci 1988;41(3–4):179–86.
[203] Benton D. Hypoglycemia and aggression: a review. Int J Neurosci 1988;41(3–4):163–8.
[204] Bolton R. Hostility in fantasy: a further test of the hypoglycemia-aggression hypothesis. Aggr Behav 2006;2(4):257–74.
[205] Lewellen TC. Aggression and hypoglycemia in the Andes: another look at the evidence. Curr Anthropol 1981;22(4):1–5. doi:10.1086/202688.
[206] Koyama K, Chen G, Lee Y, Unger RH. Tissue triglycerides, insulin resistance, and insulin production: implications for hyperinsulinemia of obesity. Am J Physiol Endocrinol Metab 1997;273(4):E708–13.
[207] Scheffel A. Serum cholesterol, triglycerides, HDL and LDL in aggressive elderly patients with dementia. Psychiatr Pol 1996;30(1):159–70.
[208] Vera Cruz EM, Brown CL. The influence of social status on the rate of growth, eye color pattern and insulin-like growth factor-I gene expression in *Nile tilapia*, *Oreochromis niloticus*. Horm Behav 2007;51(5):611–9.
[209] Barto L, Reyes E, Schams D, Bubenik G, Lobos A. Rank dependent seasonal levels of IGF-1, cortisol and reproductive hormones in male pudu (*Pudu puda*). Compar Biochem Physiol – Part A: Mol Integr Physiol 1998;120(2):373–8.
[210] Hakkak R, Shaaf S, Macleod S, Cockrell G, Korourian S. Effects of obesity on serum insulin-like growth factor 1 (IGF-1) levels using DMBA-induced ovariectomized Zucker Rat Model. FASEB J 2008;22:886.7–886.
[211] Vickers MH, Ikenasio BA, Breier BH. IGF-I treatment reduces hyperphagia, obesity, and hypertension in metabolic disorders induced by fetal programming. Endocrinology 2001;142(9):3964–73.
[212] Yakar S, Jun-Li Liu, Fernandez AM. Liver-specific igf-1 gene deletion leads to muscle insulin insensitivity. Diabetes 2001;50:1110–8.
[213] Weltman A, Weltman JY, Veldhuis JD, Hartman ML. Body composition, physical exercise, growth hormone and obesity. Eat Weight Disord 2001;6(3Suppl):28–37.
[214] Scacchi M, Pincelli AI, Cavagnini F. Growth hormone in obesity. Int J Obesity 1999;23(3):260–71.
[215] Rizza RA, Mandarino LJ, Gerich JE. Effects of growth hormone on insulin action in man. Mechanisms of insulin resistance, impaired suppression of glucose production, and impaired stimulation of glucose utilization. Diabetes 1982;31(8 Pt 1):663–9.
[216] Krag MB, Gormsen LC, Guo Z. Growth hormone-induced insulin resistance is associated with increased intramyocellular triglyceride content but unaltered VLDL-triglyceride kinetics. Am J Physiol Endocrinol Metab 2007;292:E920–7.
[217] De Felipe C, Herrero JF, O'Brien JA. Altered nociception, analgesia and aggression in mice lacking the receptor for substance P. Nature 1998;392:394–7. doi:10.1038/32904.
[218] Gregg TR, Allan S. Brain structures and neurotransmitters regulating aggression in cats: implications for human aggression. Progr Neuro-Psychopharmacol Biol Psychiatry 2001;25(1):91–140.
[219] Halasz J, Zelena D, Toth M, Tulogdi A, Mikics E, Haller J. Substance P neurotransmission and violent aggression: the role of tachykinin NK1 receptors in the hypothalamic attack area. Eur J Pharmacol 2009;611(1–3):35–43.
[220] Karagiannides I, Torres D, Tseng YH. Substance P as a novel anti-obesity target. Gastroenterology 2008;134(3):747–55.
[221] Fu Xiao-Wen, Sun Anthony M. Stimulative effect of substance P on insulin secretion from isolated rat islets under normobaric oxygen incubation. Acta Pharmacol Sinica 1989;10(1):69–73.
[222] Seegers HC, Hood VC, Kidd BL, Cruwys SC, Walsh DA. Enhancement of angiogenesis by endogenous substance P release and neurokinin-1 receptors during neurogenic inflammation. J Pharmacol Exp Therapeut 2003. doi:10.1124/jpet.103.050013.
[223] Li Q, Deng X, Singh P. Significant increase in the aggressive behavior of transgenic mice overexpressing peripheral progastrin peptides: associated changes in CCK2 and serotonin receptors in the CNS. Neuropsychopharmacology 2007;32:1813–21.
[224] Burgdorf J, Panksepp J, Beinfeld MC, Kroes RA, Moskal JR. Regional brain cholecystokinin changes as a function of rough-and-tumble play behavior in adolescent rats. Peptides 2006;27(1):172–7.
[225] Moran TH, Katz LF, Plata-Salaman CR, Schwartz GJ. Disordered food intake and obesity in rats lacking cholecystokinin A receptors. Am J Physiol – Regul Integr Compar Physiol 1998;274(73):R618–25.
[226] Ahren B, Holst JJ, Efendic S. Antidiabetogenic action of cholecystokinin-8 in type 2 diabetes. J Clin Endocrinol Metab 2000;85(3):1043–8.
[227] Kuntz E, Pinget M, Damgé C. Cholecystokinin octapeptide: a potential growth factor for pancreatic beta cells in diabetic rats. J Pancreas 2004;5(6):464–75.
[228] Schmassmann A, Reubi JC. Cholecystokinin-B/gastrin receptors enhance wound healing in the rat gastric mucosa. J Clin Invest 2000;106:1021–9.
[229] Cowey SL, Quast M, Belalcazar LM, et al. Abdominal obesity, insulin resistance, and colon carcinogenesis are increased in mutant mice lacking gastrin gene expression. Cancer 2005;103:2643–53.
[230] Atmaca M, Tezcan E, Parmaksiz S, Saribas M, Ozler S, Ustundag B. Serum ghrelin and cholesterol values in suicide attempters. Neuropsychobiology 2006;54:59–63.
[231] Tschop M, Smiley DL, Heiman ML. Ghrelin induces adiposity in rodents. Nature 2000;407:908–13.
[232] Wren AM, Seal LJ, Cohen MA. Ghrelin enhances appetite and increases food intake in humans. J Clin Endocrinol Metab 2001;86:5992–5.
[233] Pöykko SM, Kellokoski E, Hörkko S, Kauma H, Kesäniemi YA, Ukkola O. Low plasma ghrelin is associated with insulin resistance, hypertension, and the prevalence of type 2 diabetes. Diabetes 2003;52:2546–53.
[234] Tschop M, Weyer C, Tataranni AP, Devanarayan V, Ravussin E, Heiman ML. Circulating ghrelin levels are decreased in human obesity. Diabetes 2001;50:707–9.
[235] Brain PF, Nowell NW, Wouters A. Some relationships between adrenal function and the effectiveness of a period of isolation in inducing intermale aggression in albino mice. Physiol Behav 1971;6(1):27–9.
[236] Iwen KAH, Senyaman O, Schwartz A, et al. Melanocortin crosstalk with adipose functions: ACTH directly induces insulin resistance, promotes a pro-inflammatory adipokine profile and stimulates UCP-1 in adipocytes. J Endocrinol 2008;196:465–72.
[237] Morgan C, Thomas RE, Cone RD. Melanocortin-5 receptor deficiency promotes defensive behavior in male mice. Horm Behav 2004;45(1):58–63.
[238] Banno R, Arima H, Sato I, et al. The melanocortin agonist melanotan II increases insulin sensitivity in OLETF rats. Peptides 2004;25(8):1279–86.
[239] Ferris CF. Vasopressin/oxytocin and aggression. In: Gregory Bock and Jamie Goode, editors. Novartis Foundation Symposium 268 – Molecular mechanisms influencing aggressive behaviours book series: Novartis Foundation Symposia. Novartis Foundation; Published Online 5 May 2006.
[240] Bankir L, Bardoux P, Ahloulay M. Vasopressin and diabetes mellitus. Nephron 2001;87(1):8–18.
[241] Kalueff AV, Keisala T, Minasyan A, Kuuslahti M, Miettinen S, Tuohimaa P. Behavioural anomalies in mice evoked by "Tokyo" disruption of the vitamin D receptor gene. Neurosci Res 2006;54(4):254–60.
[242] Kalueff AV, Lou YR, Laaksi I, Tuohimaa P. Increased grooming behavior in mice lacking vitamin D receptors. Physiol Behav 2004;82(2–3):405–9.
[243] Holick MF. Vitamin D deficiency. N Engl J Med 2007;357(3):266–81.
[244] Borissova AM, Tankova T, Kirilov G, Dakovska L, Kovacheva R. The effect of vitamin D3 on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. Int J Clin Pract 2003;57(4):258–61.
[245] Ferron M, Hinoi E, Karsenty G, Duci P. Osteocalcin differentially regulates cell and adipocyte gene expression and affects the development of metabolic diseases in wild-type mice. Proc Nat Acad Sci USA 2007;205:5266–70.
[246] Lee SJ, McPherron AC. Regulation of myostatin activity and muscle growth. PNAS 2001;98(16):9306–11.
[247] Hittel DS, Berggren JR, Shearer J, Boyle K, Houmard JA. Increased secretion and expression of myostatin in skeletal muscle from extremely obese women. Diabetes 2008. doi:10.2337/db08-0943.
[248] McPherron AC, Lee SJ. Suppression of body fat accumulation in myostatin-deficient mice. J Clin Invest 2002;109:595–601. doi:10.1172/JCI200213562.
[249] Sandoval DA, Obici S, Seeley RJ. Targeting the CNS to treat type 2 diabetes. Nat Rev 2009;8:386–98.