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"Infectobesity: viral infections (especially with human adenovirus-36: Ad-36) may be a cause of obesity

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SUMMARY

In recent years viral infections have been recognized as possible cause of obesity, alongside the traditionally recognized causes (genetic inheritance, and behaviour/environmental causes such as diet exercise, cultural practices and stress). Although four viruses have been reported to induce obesity (infectoobesity) in animal models (chickens, mice, sheep, goat, dogs, rats and hamsters), until recently the viral etiology of human obesity has not received sufficient attention, possibly because the four viruses are not able to infect humans. In a series of papers over the last ten years, however, the group of Prof. Dhurandhar (Pennington Biomedical Research Center, LA, USA) demonstrated that a human adenovirus, adenovirus-36 (Ad-36), is capable of inducing adiposity in experimentally infected chickens, mice and non-human primates (marmosets). Ad-36 is known to increase the replication, differentiation, lipid accumulation and insulin sensitivity in fat cells and reduces those cells' leptin secretion and expression. It also affects human primary preadipocytes. In rats increased adiposity was observed due to Ad-36 infection. Recent studies have shown that, in the USA, antibodies to Ad-36 were more prevalent in obese subjects (30%) than in non-obese subjects (11%). We postulate that Ad-36 may be a contributing factor to the worldwide rising problem of obesity. We suggest the extension of comparative virological studies between North America and Europe, and studies between discordant twins (both dizygous and monozygous).

Introduction

In western countries obesity is major problem. In the United States alone 25% of the adult population are obese (i.e. have a Body Mass Index [BMI] > 30), and more are overweight (BMI >25; Fig. 1). Furthermore, obesity is not only a problem for adults, but also for an increasing number of children; in the United States over 20% of children have been diagnosed as obese [1,2]. This problem also increasing; in the United States, estimates of overweight prevalence over time indicate dramatic increases in all race groups in both men and women [1,2]. Between two survey periods (1976–1980 and 1988–1991), overweight prevalence increased by 8%, the mean body mass index for adults aged 20 through 74 years increased from 25.3 to 26.3, and the mean body weight increased by 3.6 kg [3]. Overweight or obese people have a significantly higher risk of serious health problems, such as cardiovascular disease [4]. Fig. 1 details the increase of overweight prevalence in children in the United States across four survey periods from 1971 to 2001. Lakka et al. [5] suggested that the increase in prevalence due to changes in lifestyle and diet, combined with genetic susceptibility. Fig. 2 shows the increase in morbid obesity (BMI > 40) in adult males and females from the United States and United Kingdom. In both countries females show a faster increase than males, and the United States shows faster rates of increase than the United Kingdom.

Alongside this increase in overweight and obesity prevalence, western countries have seen a rise in metabolic syndrome. It is estimated that, in the US, over 47 million people or 25% of the population is affected [6]. Symptoms can include obesity, with related type 2 diabetes [7], metabolic syndrome insulin resistance [8], and the deposition of triglycerides in the liver. Deposition of triglycerides is, in turn, strongly associated with non-alcoholic fatty liver disease (NAFLD), a disease spectrum from hepatic steatosis, to steatohepatitis, fibrosis and cirrhosis [9].

People with metabolic syndrome also have increased risk of coronary heart disease and other diseases related to plaque build-ups in artery walls (e.g., stroke and peripheral vascular disease). The etiology of metabolic syndrome is unclear; often there are many factors interacting (Fig. 3), such as age, genetic susceptibility (thrifty genes, diabetic history, race), environmental factors related to life style (psychology, smoking, exercise, culture, stress, diet), and possibly viral infections.

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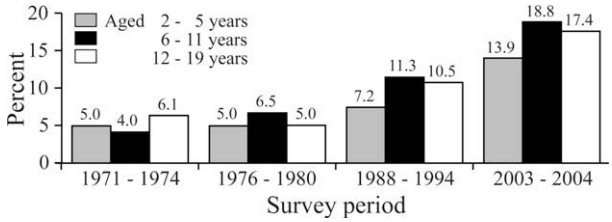

Fig. 1. Overweight prevalence among U.S. children and adolescent (Aged 2–19 years). Data from the National Health and Nutrition Examination Surveys (NHANES; [1,2]).

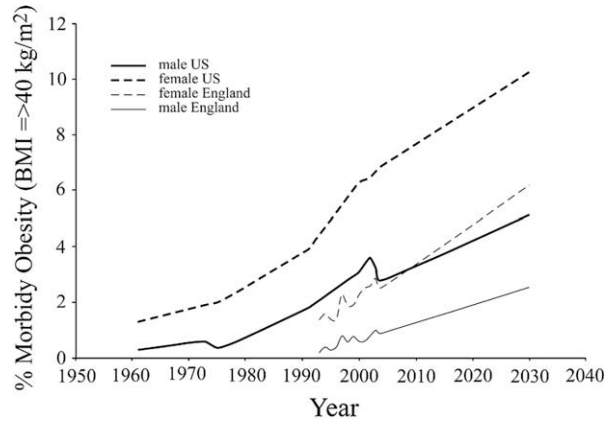

Fig. 2. The rise in morbid obesity in the UK (top) and the USA (bottom). Data Lobstein, T. (2007). Obesity-International Comparisons URN 07/926A1; Prevalence, co-morbidities, diet, physical activity, economic drivers, prevention strategies and governmental policies, University of Sussex, R Jackson Leach, International Obesity Taskforce.

Viruses and obesity in animal models

Canine distemper virus (CDV)

This paramyxovirus (related to the human measles virus) is known to cause severe health problems in dogs and various carnivorous mammals, including respiratory, gastrointestinal and central nervous system diseases. The virus replicates in the neurons and glial cells of the white matter of the brain. CDV has been found to induce obesity in inoculated mice [10], with increased body weight and fat-cell size. The mice also showed reduced circulating catecholamine levels and hypothalamic damage (which was not caused by peripheral dysfunction). CDV induces changes in brain morphology [11,12], and Bernard et al. [13] found viral mRNA in the hippocampus, entorhinal cortex, mesencephalon and the hypothalamus of infected mice. The hypothalamus plays an important role regulating appetite, energy consumption and neuroendocrine functions [14]. One change is a decrease in the number of leptin receptors in the hypothalamic area of the brain and an increase in those of the cortex and hippocampus [14]. Leptin is an adipocyte secreted hormone which is involved in body weight regulation. It also enhances proliferation and activation of circulating T-cells and it stimulates cytokine production. After leptin is secreted into the bloodstream, it enters the brain and has an effect on the adipose tissue mass. When a large amount of adipose tissue is present, more leptin is secreted, which in turn results in a loss of appetite [15]. When fewer receptors are present in the hypothalamus, hunger may be induced despite the presence of fat cells.

Rous-associated virus-7 (RAV-7)

This avian retrovirus has been reported to cause obesity, hyperlipidemia and hypercholesterolemia in chickens, along with fatty, yellow-coloured and enlarged livers [10]. The livers of infected chickens, weighed 2.5 times those of the controls. It is suggested that the RAV-7 induced obesity by reducing thyroid hormone levels, probably via the liver, but the exact mechanism remains unclear.

Borna disease virus (BDV)

BDV is a single, negative stranded RNA virus of Order Mononegavirales, genus *Bornaviridae*. It primarily targets the nervous system, but it also replicates in other organs. Infection provokes a strong immune response, but the virus remains in the nervous system. BDV causes encephalomyelitis in horses and sheep, and laboratory experiments show that birds, rodents and primates can also be infected [10]. In rats the virus causes 'Induced Obesity Syndrome', with lympho-monocytic inflammation of the hypothalamus, hyperplasia of pancreatic islets and elevated serum glucose and triglyceride levels [10]. The severity of the syndrome varies with viral strain used, genetic background of the animal and the age at inoculation

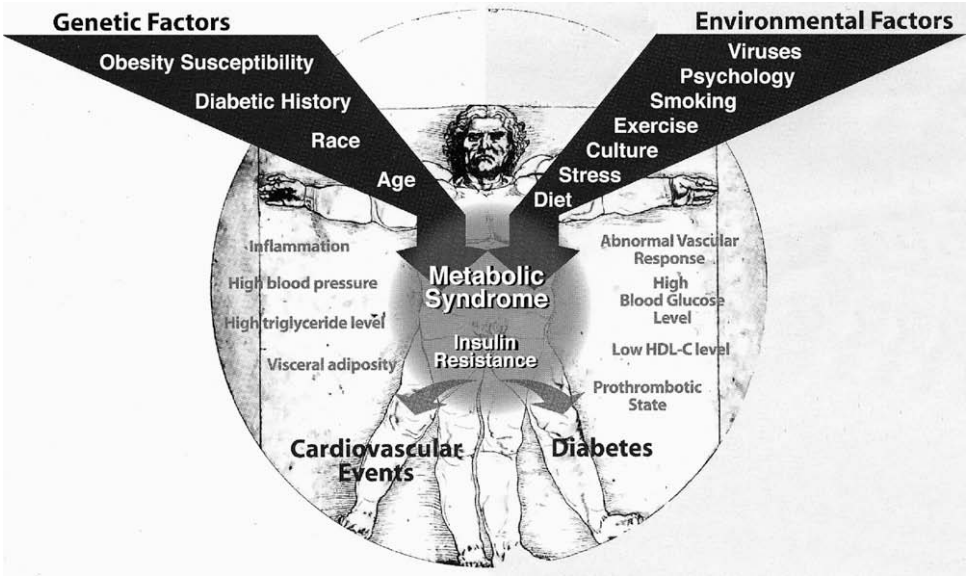

Fig. 3. Genetic and environmental factors which may lead to Metabolic Syndrome.

(progressive disease when newborns are inoculated and acute encephalitis in inoculated adults). Infected rats with the obese phenotype show inflammatory lesions in different regions of the brain (septum, hippocampus, amygdala and ventromedian tuberal hypothalamus). It is therefore likely that the obesity is caused by neuroendocrine dysregulations; the inflammatory lesions may affect sites in the brain which are involved in body weight regulation and food intake. BDV antigen and antibodies have been seen in human brains at autopsy, and are associated with schizophrenia and mental depression. However, there is as yet no proof that BDV causes obesity in humans.

Scrapie agent

This prion causes a neurodegenerative disease ('scrapie') with a long incubation period in sheep and goats [10]. This infection produces vacuoles in the cerebellum and white matter and leads to abnormal behaviour and motor dysfunction (the name is derived from the characteristic 'scraping' behaviour seen in infected animals). Some scrapie strains can also cause obesity in inoculated mice and hamsters. For example, the ME7 strain induces obesity and vacuolisation in the forebrain of the mice. Adrenalectomy prevents obesity in these cases, suggesting that the disease acts via the hypothalamic-pituitary-adrenal axis. In recent research [16] is found that different brain regions show reduced glucose tolerance after scrapie infection. The scrapie agent is thought to be closely related to the prions causing Bovine Spongiform Encephalopathy (BSE) and Creutzfeld–Jacob's disease [17,18].

SMAM-1

This is an avian adenovirus which caused a poultry epidemic in India during the 1980s. It is probably transmitted via aerosols, which makes it highly contagious, and it is likely that SMAM-1 is spreading beyond the borders of India. The virus is serologically similar to chick embryo lethal orphan (CELO) virus. In experiments with chickens, excessive visceral fat and lower levels of serum lipids were found. Enlarged liver and kidneys, hepatic fatty infiltration and congestion and basophilic intranuclear inclusion bodies in hepatocytes were also observed. Even though the infected animals had the same food intake as the control group, the inoculated group had a lower body weight and a higher amount of visceral fat. Until recently, it was thought that this avian virus could not infect humans, but research [19] showed that 20% of obese humans had antibodies to SMAM-1. These individuals also had lower serum cholesterol and triglycerides. The underlying mechanism is yet to be uncovered.

Adenoviruses

The adenovirus family is a large family of naked, DNA containing viruses, with a symmetrically icosahedral shape and a diameter ranging from 65–80 nm (Fig. 4). Adenoviruses replicate in the nucleus of the infected cell [20]; the genome is commonly consists of 36 kb pairs of linear double stranded DNA. Fifty human adenovirus serotypes have so far been described [21] and they have been classified into six sub-groups, A–F.

The virus can be transmitted very easily via respiratory, droplet, venereal and fecal–oral routes (the viruses can often be isolated from nasal swabs and feces). Adenoviral infections often affect the upper respiratory tract (the name is derived from the adenoids, or pharyngeal tonsils, where the first adenovirus was discovered), but they can also be responsible for more serious symptoms such as enteritis and conjunctivitis. Some adenovirus species can give a persistent asymptomatic infection, while others lead directly to symptoms and are promptly destroyed by the immune system of healthy individuals. No treatments are known for adenoviral infection, but the symptoms can be treated; vaccines have been developed for two adenoviruses (Ad-4 & Ad-7).

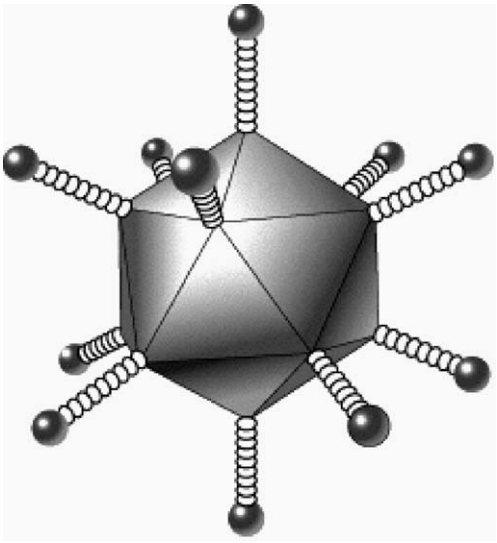

Fig. 4. A schematic drawing of the icosahedral structure of adenoviruses.

Adenovirus-36

Adenovirus-36 (Ad-36) belongs to subgroup D along with Ad-9 and Ad-37 [21,22] (Table 1). It is antigenically distinctive from other human adenoviruses, and does not cross-react with them. The virus was first isolated from a 6 year old diabetic German girl, who suffered from enteritis [23].

Recently Ad-36 infection has been linked with obesity in animal models and in humans. Symptoms include an increase in adipose tissue combined with low levels of serum cholesterol and triglycerides (e.g. [19,24,25]. Furthermore, experiments on preadipocytes [21] suggest that these may be 'hit and run' effects [26]; after the initial infection, neither viral DNA replication nor Ad-36 mRNA expression are required to maintain an increased level of preadipocyte differentiation. However, the mechanism underlying this phenomenon remains unclear.

The following sections review the research to date on the link between Ad-36 and obesity (in Table 2).

Animal research on Ad-36

Dhurandhar et al. [24] published the first article on *in vivo* studies of the obesity stimulating capacities of Ad-36. Three experiments were conducted on chickens and one on mice.

In the first experiment 39 SPF chickens were monitored for their ad libitum food and water intake. After 3 weeks the chickens were divided into three weight-matched groups. Blood was drawn for baseline measurements of serum cholesterol and serum triglycerides. One group was inoculated with Ad-36, one control group was injected with a sterile media, and a second control group with Chick Embryo Lethal Orphan virus (CELO). CELO is an avian adenovirus that is serologically similar to SMAM-1, but which has not been linked to obesity. The chickens were sacrificed three weeks after inoculation. Both the Ad-36 and CELO group showed raised titers of antibodies to their respective virus, while no rise in antibody titers was found in the control group. For all three groups

Table 1
The classification of adenovirus 36 [22].

Group:	Group I (dsDNA)
Family:	*Adenoviridae*
Genus:	*Mastadenovirus*
Species:	*Human adenovirus D* (HAdV-D)
Serotype:	Human adenovirus-36 (HAdV-36)

Table 2
Effects of Ad-36 inoculation on different animal species.

Species	Body weight*	Visceral fat*	Total body fat*	Serum cholesterol*	Serum triglycerides*	Food intake*	Ad-36 DNA	Sources
Chickens	=	+	+	–	–	=	Blood and visceral fat	[24]
Mice	+	+	+	–	–	=	–	[24]
Rhesus monkeys	+	–	–	–	–	–	–	[28]
Marmoset monkeys	+	+**	+	–	–**	–	Adipose tissue, liver, skeletal muscle, lung, brain	[28]
Hamsters total	+	–	–	=	–	=	Visceral adipose tissue, liver, lung, skeletal muscle	[29]
Hamsters normal diet	+	–	–	=	–	=	–	[29]
Hamsters fat diet	=	–	–	=	–	=	–	[29]
Human	+	+	–	–	–	–	–	[25]
Human twins	+	+	–	=	=	–	–	[25]

No data present.
* Compared to the control groups.
** Not significant.

the food intake was equal, and the body weights between groups were equal at time of sacrifice. However, visceral fat and total body fat were significantly greater in the Ad-36 group (100% greater than in the sterile media control group). The Ad-36 group also showed serum triglyceride values and serum cholesterol which were lower than in the control group. In the CELO group only the serum triglycerides were significantly lower than in the control group.

In the second experiment 16 male SPF chickens Ad-36 was inoculated intranasally, and a control group were inoculated with sterile media. These chickens were sacrificed five weeks after inoculation. Ten of the 16 Ad-36-inoculated chicks had Ad-36 antibodies, and viral DNA was found in visceral fat but not in muscle tissue. The food intake and body weight was similar between the test and control groups but visceral fat was found to be 128% greater and the total body fat 46% greater in the Ad-36 group. Serum cholesterol and triglycerides were also both significantly lower in the Ad-36 group.

The third experiment repeated the second experiment but with intraperitoneal inoculation. Ten chicks were inoculated with Ad-36 and eight chicks were inoculated with sterile medium. Thirteen weeks after inoculation the chicks were sacrificed. All Ad-36 inoculated chicks possessed antibodies against Ad-36; viral DNA was found in the visceral fat of the infected chickens. The body weight and food intake were equal between the groups and the visceral fat was 74% greater in the Ad-36 group than in the control group. The serum cholesterol and triglycerides were not significantly lower. No differences in brain histopathology were found.

In the fourth experiment twenty mice were intraperitoneal inoculated with Ad-36 and a control group of ten mice were inoculated with sterile medium. Both groups had *ad libitum* access to food and water. After 22 weeks 19 of the Ad-36 inoculated mice had raised antibodies to Ad-36, and their body weight was 9% greater, total body fat 35% greater, and visceral fat 67% greater than that of the control group. In common with the experiments on chicks, serum cholesterol and triglyceride levels were both significantly lower (38% and 31%, respectively) in the Ad-36 group than in the control group. Dhurandhar et al. [24] did not find any morphological changes in the brain resulting from Ad-36 infection. However recently, it was demonstrated in rats that human Adenovirus-36 indices adiposity, increases insulin sensitivity, and alters hypothalamic monoamines in rat brain [27].

In other experiments Dhurandhar et al. [23] investigated the transmissibility of Ad-36. In one experiment uninfected chickens were housed with Ad-36 infected chickens. After 12 h blood was drawn and capillary electrophoresis was performed to screen for the presence of Ad-36 DNA; all the uninfected chickens had become infected. In another experiment uninfected chicks were injected with blood from infected chickens. All the injected chickens raised antibodies to Ad-36, as well as an increase in visceral fat and total body fat, and lower serum cholesterol, than a control group.

In male rhesus monkeys with naturally occurring Ad-36 antibodies, a weight gain and a decrease of plasma cholesterol levels was seen after 36 months [28]. In three male marmoset monkeys, which were inoculated with Ad-36, a threefold weight gain, a fat gain and a lowering of serum cholesterol was seen compared to uninfected controls [28].

Kapila et al. [29] examined the effect of Ad-36 on hamsters. One group was inoculated with Ad-36 and a control group with sterile medium. Half of the animals in each group were fed on a normal diet while the other half was put on a high-fat diet. After sacrifice, antibodies against Ad-36 were found in the inoculated group, and Ad-36 DNA was detected in the lungs, liver, visceral adipose tissue and skeletal muscle. Plasma cholesterol was equal for the inoculated and control groups, but in the inoculated group (both those on normal and high-fat diets) LDL cholesterol was a larger proportion of the lipoproteins that were isolated by density gradient ultracentrifugation. No further information was given on the implications of this cholesterol change.

Recently *in vitro* and *ex vivo* studies in rats demonstrated that Ad-36 modulates adipocyte differentiation, leptin production and glucose metabolism [30].

Human studies on Ad-36

One human cohort study has been conducted [25]. The serum of obese (BMI>30, $n = 360$) and non-obese ($n = 142$) volunteers from three American cities (Madison WI, Naples FL, and New York NY) was analysed for the presence of Ad-36 antibodies, and serum triglyceride and serum cholesterol were measured. The mean age of the non-obese group was less than that of the obese group ($P < 0.001$), but the mean age for Ad-36 antibody positive subjects was similar to that of the Ad-36 negative subjects. Ad-36 antibodies were found in 30% of obese and 11% of non-obese subjects. In both the obese and non-obese groups the mean BMI was greater and serum cholesterol was higher in the Ad-36 positive group than in the Ad-36 negative group ($P < 0.0001$). Serum triglycerides were only measured at the Wisconsin site, fasting people. In the obese subjects the serum triglycerides were significantly lower ($P < 0.0001$) in Ad-36 antibody positive people compared with the Ad-36 antibody negative people.

Atkinson et al. [25] have also conducted a twin study. The serum of 89 twin pairs was checked for Ad-36 DNA and antibodies. 26 twin pairs (20 monozygotic and 6 dizygotic) were discordant for Ad-36 antibody presence. Of these twins the BMI was measured, and blood samples were analysed for serum cholesterol and triglyceride levels. These subjects also had a body fat measurement using dual-energy X-ray absorptiometry, hydrodensitometry, and/or bioimpedance analysis. The Ad-36 positive individuals were found to be heavier and fatter than their Ad-36 negative sibling. Antibody positive subjects had a mean BMI of 26.1 compared with 24.5 for the control group ($P < 0.04$) and the mean total body fat

was 29.6 compared with 27.5 in the control group ($P < 0.04$). No differences in serum cholesterol and triglycerides were found.

Prevalence of Ad-36 antibodies in human populations may vary by the geographic location. Only five percent of the subjects screened in Denmark had antibodies to Ad-36 [31]. In the introduction the observation is made that obesity is a larger problem in the USA in comparison to the UK (Europe) and is rising more rapidly in the USA (Fig. 2). Comparison in epidemiology might be an interesting suggestion for future research.

Hypotheses

Animals inoculated with Ad-36 show a higher fat percentage combined with low levels of serum cholesterol and triglycerides. The only other virus known to induce these symptoms is avian adenovirus SMAM-1 (see above). Unfortunately, the underlying mechanism causing these symptoms remains unknown. Below, we postulate hypotheses on four possible mechanisms, which may act alone or in combination.

Hypothesis 1: Food intake

The Ad-36 virus might induce changes in the brain or body, which lead to food cravings. However, in animal studies Ad-36 inoculated animals did not eat more food than the control group given food ad libitum. We therefore hypothesize that an increase in food intake is unlikely to be the main cause of Ad-36 induced obesity.

Hypothesis 2: Changes in brain morphology

Dhurandhar et al. [24] did not find any morphological changes in the brain resulting from Ad-36 infection, suggesting that the mechanism causing obesity is different from that seen in CDV infection. Viral DNA has been isolated in the brains of infected marmosets, although its effects (if any) are unknown. Recently it was demonstrated that Ad-36 induces increases in insulin sensitivity, and alters hypothalamic monoamines in rats [27]. We hypothesize, therefore, that obesity in infected individuals may be caused by changes in brain chemistry.

Hypothesis 3: Liver abnormalities

One of the most important organs in lipid metabolism is the liver. It is therefore likely that Ad-36 has an influence on its functioning and performance. However, no morphological alterations have been reported as a result of Ad-36 infection, nor have any chemical changes been discovered.

Other viruses are known to cause liver damage, which often lead to problems with the lipid metabolism. The best-known is the hepatitis C virus (HCV), which causes non-alcoholic fatty liver disease (NAFLD). This syndrome starts with hepatic steatosis, or fatty liver (found in 50% of HCV patients; [32]), and ends with liver fibrosis and liver dysfunction, which may eventually lead to death.

Therefore, we hypothesize that Ad-36 may induce changes in the liver, which may in turn cause (or reinforce) changes causing obesity.

Hypothesis 4: Adipose tissue

Until recently, adipose tissue was seen as a passive tissue, but it is now known to function as an endocrine organ; adipocytes secrete leptin, a signalling hormone which eventually leads to a decrease in appetite. Besides leptin, the adipocytes also secrete many other cytokines, which influence other adipocyte and preadipocyte cells. In obesity, TNF-α is secreted by adipose tissue, and this may be responsible for insulin resistance [15]. In obese individuals increased levels of interleukin-6 (IL-6) and C-reactive proteins were observed; these hormones are involved proliferation, differentiation, apoptosis, and development [33]. IL-6 is not only secreted by adipocytes, but also by macrophages, and it induces an early inflammatory response at sites of infection. This may mean that fat tissue has a role in immune response. The highest cytotoxic potential was found in inguinal white adipose tissue. Interscapular brown fat tissue had a low cytotoxic ability [34].

Recently it was shown that preadipocytes have the ability to phagocytose like macrophages [35], and also show antimicrobial activity. This indicates that preadipocytes might actually function as a part of the immune system, although no proof this is yet to be demonstrated.

Vangipuram et al. [36] observed preadipocytes differentiate when infected with Ad-36 (3T3- L1 cells, murine preadipocyte cell line). This mechanism might contribute to the obesity promoting abilities of Ad-36, as it increases the number of adipocytes. However this cannot account for the changes in serum cholesterol and serum triglycerides and the enlargement of the adipocytes. The underlying mechanism by which the preadipocytes are stimulated to differentiate is still unclear. We hypothesize it is linked to the possible role of this tissue in the immune system, as a reaction to viral infection.

Discussion

Suggestions for further research

Human cohort study and twin study: We suggest that light could be shed on the role of Ad-36 infection in human obesity by using data from The Rotterdam Study (The Netherlands), a study of over 8000 people who have been followed for over 12 years. Blood samples of people with a sudden weight change could be analysed for the presence of Ad-36 antibodies, serum triglycerides and serum cholesterol. With these data, patterns of infection can be determined. Because this is a follow-up study over a long period of time, information can be gained about the progression of the illness, and whether its effects are reversible. The HFSP (Human Frontiers of Science, Amsterdam, The Netherlands) twin study (528 DZ twins and siblings of twins and 265 MZ twins) would also be useful. Blood samples of twins could be analysed for the presence of Ad-36 antibodies. The data of discordant twin pairs can be further investigated. Weight, BMI, serum cholesterol and serum triglycerides could be linked with the presence of Ad-36 antibodies. Because the study has recorded so much information on the twins in the study group, many confounding factors (age, sex, personal history etc.) could be eliminated.

Changes in adipocytes and preadipocytes

More animal research is needed to uncover the mechanism of obesity induced by Ad-36 virus infection. A key question is the mechanism by which the virus changes adipocytes and preadipocytes and their secreted products. These tissues are important because they might be directly involved in the immune response against the virus, as well as in the observed changes in body fat and serum cholesterol and triglyceride levels.

Genetic factors preventing Ad-36 induced obesity

Not all individuals infected by Ad-36 are overweight [25]. However, this observation and its link to adiposity has not been explored in detail. It is possible that certain genetic factors increase or decrease susceptibility to Ad-36 induced obesity.

Vaccine and cure

If Ad-36 is a significant factor in the widespread increase in obesity, it is clear important to investigate possible vaccines to prevent infection, or treatments to alleviate the effects once infected. Vaccines already exist against two adenoviruses (Ad-4 and Ad-7).

In conclusion, infectoobesity would be an extremely significant concept, if shown to be relevant to humans; particularly, a good understanding of Adenovirus-36 would be needed for better management of obesity. This could lead to the possibility to prevent or treat a factor causing obesity in the human population.

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