Neuroendocrine Abnormalities in Human Obesity

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Recent research has indicated that visceral obesity is associated with multiple endocrine disturbances. Insulin resistance, as well as visceral fat accumulation, may be consequences of these abnormalities. The complex endocrine aberrations are probably of central origin, and suggest a neuroendocrine background with a "hypothalamic arousal" syndrome. Such a syndrome has been found after excess alcohol intake, tobacco smoking, and certain types of stress reactions. Subjects with visceral obesity might be characterized by a high prevalence of such factors, although only indirect evidence is available for the stress component, maybe caused by a poor socioeconomic and psychosocial situation. In primate experiments, a submissive stress reaction is followed by a syndrome essentially identical to that seen in humans with visceral obesity, including visceral fat accumulation. These observations strongly support a similar chain of events in humans. Recent studies have indicated several abnormalities in cerebrospinal fluid (CSF) concentrations of catecholamines and neuropeptides. In particular, serotonin metabolites and corticotropin-releasing factor (CRF) concentrations are apparently lower than normal. In women with visceral obesity, these low concentrations are associated with food choices that indicate a preference for carbohydrates. This finding emphasizes the importance of serotonin agonists in the treatment of human obesity. It seems possible that such drugs may have effects on metabolic and other symptoms particularly prevalent in abdominal obesity, and that these effects might be independent of the decrease in energy intake. It would seem highly desirable to explore these possibilities further. Such observations may also provide a link between the abnormalities of low serotonin and CRF concentrations in the central nervous system on one hand and peripheral metabolic and other abnormalities on the other.

IT IS NOW WELL ESTABLISHED that human obesity is followed by several endocrine abnormalities. These include an increased turnover of cortisol and a low secretion of sex steroid hormones and growth hormones. Insulin resistance is a common associate and may well be a consequence of the aberrations of steroid hormone secretion in combination with an increased flux of free fatty acids, which affect both muscle and liver metabolism. All these perturbations seem more pronounced in visceral (abdominal, central, or android) obesity than in peripheral (gluteofemoral or gynoid) obesity. It has also been postulated that the centralization of body fat stores in visceral obesity might be caused by the multiple endocrine abnormalities.[1]

Insulin resistance, a major metabolic perturbation of visceral obesity, has been considered to provide a basis for several other metabolic abnormalities[2] often found in visceral obesity, which include hyperlipidemia and hypertension.[1,3] These abnormalities are established risk factors for cardiovascular disease (CVD), stroke, and non–insulin-dependent diabetes mellitus (NIDDM), which constitute what is now commonly called the metabolic syndrome. Visceral obesity, as estimated by the waist to hip ratio (WHR), is by itself an independent risk factor for CVD and stroke, and in association with body mass index (an estimation of total body fat mass), it is also a risk factor for the development of NIDDM.[4] Taken together, this probably means that the elusive relationship between obesity on one hand and CVD and stroke on the other is mainly explainable by associations between the subgroup of visceral obesity and the disease end points. This might be accomplished by mechanisms that generate the metabolic risk factors for CVD, stroke, and NIDDM.[5]

The chain of events that lead to CVD, stroke, and NIDDM may thus start with the multiple endocrine perturbations that generate insulin resistance and other metabolic risk factors for disease, which in turn are connected to the precipitation of the diseases. There is considerable evidence from clinical studies, which include intervention trials, and mechanistic research at the cellular and molecular level that the presumed chain of events might be correct.[1,4] This then places the endocrine abnormalities in focus for further pathogenetic considerations.

As mentioned earlier, the endocrine abnormalities of visceral obesity pertain to cortisol, sex steroid hormone, and growth hormone secretions. In addition, there seem to be fewer well-defined disturbances in the central regulation of the sympathetic nervous system. Cortisol and sympathetic nervous system abnormalities can be elicited or amplified by mental and physical stressors.[6,7] Sex steroid and growth hormone secretions are centrally regulated. These observations, taken together, indicate dysregulations of the hypothalamo-adrenal and -gonadal axes, as well as disturbances in the central regulations of growth hormone secretion and the autonomic nervous system. These multiple abnormalities in the regulation of peripheral endocrine and nervous events strongly suggest a role for central neuroendocrine dysregulation. Similar abnormalities have been repeatedly described in animal experiments as a consequence of a "hypothalamic arousal" syndrome.[8]

Such a syndrome has been found to be a consequence of response to stress, and may also be induced by tobacco smoking and excess alcohol intake.[9,10] It is interesting that in a nonselected population, subjects with a high WHR smoke more often and have a higher-than-average alcohol consumption.[11,12] These studies also showed other results of potential importance concerning this relationship. Subjects with a high WHR are often on sick leave and absent from

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work with diseases of presumed psychosomatic origin such as peptic ulcers and gastrointestinal bleeding. Generally, they also use free healthcare services more often, and even more specifically, frequently consume psychotropic drugs, including anxiolytics and antidepressants. These observations might be signs of a poor ability to cope with stress, of which the endocrine abnormalities may well be an ingredient. These observations agree with animal data that show that deficient coping with stressful situations is followed by similar consequences.[8]

Further examinations in human population studies showed than an elevated WHR is associated with a low educational level, employment in physical-type work, which suggests unskilled work, and relatively low income.[11,12] It may then be speculated that such persons are trapped in a psychosocial and socioeconomic situation where they are often subjected to stressful situations with which they have difficulties in coping. The consequences might be psychosomatic and psychiatric diseases, as well as an increased use of alcohol and tobacco, and a hypothalamic arousal syndrome with its multiple, peripheral endocrine consequences. Another presumed consequence that has been observed is an increased sensitivity to laboratory stress.[6,7]

It is of considerable interest that subjects with obesity (increased body mass index), in whom the WHR was adjusted for, had few of these abnormalities. In fact, the observations suggested that obesity per se is found in subjects who are often characterized by negative scores for the factors mentioned. People with generalized obesity were thus found to be well adapted to their psychosocial and socioeconomic environment.[11,12] However, it should be emphasized that severe obesity was not highly prevalent in the cohorts examined. These relationships might well be different with severe obesity.

Another note of interest in this connection is that several studies have indicated that psychosocial factors are related to the risk for CVD.[13] The connection between such factors and somatic disease has been elusive, perhaps due to the fact that studies have been performed on the psychosocial environment or on the somatic risk factor pattern but seldom on a combination of both psychosocial and somatic factors. A neuroendocrine response, followed by peripheral endocrine and metabolic perturbations, might provide a link between psyche and soma, which would then be followed by disease. Accumulation of visceral fat would presumably be another consequence. If this is correct, then the measurements of body fat distribution, as provided by the simple WHR, might give an indication of such a psychosomatic interaction.[14]

Cross-sectional evidence thus suggests a coupling between the neuroendocrine abnormalities discussed and psychosocial and socioeconomic handicaps, which leads to stress reactions due to poor coping. Such observations have recently been confirmed in other studies.[15,16] It seems exceedingly difficult to obtain more conclusive evidence by performing other types of studies in humans. For example, interventional studies, where humans are subjected to uncontrollable stress situations for a prolonged period of time, are obviously not possible for ethical reasons. Recording psychosocial stress factors with subsequent evaluation of the psychosomatic consequences would also be a difficult experiment to perform, because it would require major psychosocial interventions in large populations for a prolonged period under controlled conditions.

However, such longitudinal observations are possible to perform in experimental animals. As mentioned earlier, there is substantial literature on the endocrine consequences of prolonged stress of different types in animal experiments.[8] When animals are subjected to stress, some individuals cope with the challenge via a fight-or-flight reaction, striving to reach control. If control is achieved, the endocrine consequence is an increased activity along the sympathetic nervous system axis, and testosterone secretion is elevated in dominant males. In individuals who cannot cope with the challenge, a depressive, uncontrollable situation will prevail; the resulting endocrine consequence is an increased activity along the hypothalamo-adrenal axis, with the peripheral consequence of an elevated cortisol secretion. Concomitantly, sex steroid hormone secretions are blunted. This has been observed in several species, which include primates.[8,17] The area of the brain where these events are regulated is essential for survival and can be traced through species, including humans. However, in humans, the primitive psychologic reactions are masked by a multitude of overriding factors, which include upbringing, education, and social acceptability. However, the neuroendocrine consequences may not be controlled, and are most likely similar to those in species of lower rank.[18]

Observations in primates are of particular interest in this regard. In a series of studies, monkeys have been subjected to standardized laboratory stress and endocrine and metabolic consequences were evaluated for prolonged periods. The reaction pattern of either the fight-or-flight type or the submissive, uncontrollable type, as described before,[8] has been confirmed in both behavioral and neuroendocrinologic terms. Furthermore, in these studies, metabolic consequences of the submissive stress reaction have been evaluated in detail and include insulin resistance with a tendency for decreased glucose tolerance, hyperlipidemia, and hypertension. Coronary atherosclerosis also develops. Recent studies have also shown that such animals accumulate visceral fat.[19,20] It is thus apparent that a syndrome essentially identical to that of visceral obesity in humans has been elicited by the introduction of stress, leading to a reaction of poor coping and submission. These observations strongly suggest that the presumed chain of events in humans is similar, although cross-sectional evidence available in humans is only suggestive as far as the influence of stress is concerned.

The multiple endocrine abnormalities observed in human visceral obesity thus suggest a central, neuroendocrine perturbation as a common link. To establish further such a link, we considered it ethically possible to seek further evidence along this line. A more direct way to accomplish this is to examine concentrations of catecholamine metabolites and neuropeptides in cerebrospinal fluid (CSF). We balanced the potential benefit of such information against the usually minor discomfort of lumbar puncture when

performed by skilled hands. Since subjects with visceral obesity are at risk of developing severe serious diseases, further information on pathogenetic factors is of obvious importance. We embarked on this study taking this knowledge into account. In addition to measurements of CSF components, a number of endocrine, metabolic, and behavioral factors were measured and recorded, including detailed appetite and food preferences during repeated periods of the day.

Results of these studies have shown several abnormalities in the concentrations of catecholamine metabolites and neuropeptides in CSF of obese patients as compared with controls. The results are still preliminary because control data are not optimal. The controls were sex- and age-matched, non-obese, normal subjects, but analyses were not performed in the same assay batches. However, some of the abnormalities are so pronounced that they will probably hold in further controlled comparisons. Relationships with behavioral observations support this assumption, as will be described hereafter.

The most pronounced abnormalities in CSF were low concentrations of 5-hydroxyindoleacetic acid (5-HIAA), a serotonin metabolite, and corticotropin-releasing factor (CRF); these values intercorrelated strongly. There were no differences in concentrations measured in women with peripheral or visceral obesity. However, these two types of obesity differed in several aspects. In women with an elevated WHR, there were strong negative relationships between 5-HIAA or CRF concentrations and measurements of carbohydrate preferences in food intake and appetite recordings. Such relationships were absent in women with peripheral obesity. In fact, these preferences were positively correlated with WHR, but not with body mass index. Furthermore, only in women with an elevated WHR were there significant correlations between 5-HIAA and CRF, as well as endorphins.

The significance of these results is not entirely clear. First, it may obviously be questioned to what extent measurements of concentrations of catecholamine metabolites and neuropeptides in CSF collected at the lumbar level reflect the concentration present in the neighborhood of the third ventricle. However, the relationship to independent measurements of food intake behavior suggests that at least the 5-HIAA and CRF results are relevant.

Comparisons between women with visceral and peripheral obesity revealed no striking differences in most of the measured CSF variables. However, clear differences were found in the interrelationships between CSF neuropeptide concentrations, which were only found in women with a high WHR. Furthermore, negative relationships between 5-HIAA levels and carbohydrate preferences were also found only in such women, who were generally more prone to consume carbohydrates. These preliminary observations suggest that a low 5-HIAA concentration in women with abdominal obesity is associated with carbohydrate intake. The interrelationships between CSF neuropeptides, in these women only, may also suggest differences in the connections between neuropeptide secretions or a turnover between visceral and peripheral obesity.

Low CRF values in CSF are surprising in light of apparent functional oversecretion of cortisol in women with visceral obesity elicited by laboratory stress.[6] Although several of the women experienced severe headaches after the lumbar puncture, the procedure itself, performed by an experienced internist or neurologist, was associated with only minor discomfort. An objective measurement of this was obtained by the fact that cortisol excretion did not change during the procedure. It may therefore be considered that an elevated CRF level might be found only during a stress challenge of a more severe nature than lumbar puncture. Alternatively, CRF levels may be higher in areas of the brain that regulate corticotropin-cortisol secretions but lower in other centra where CRF is produced, resulting in a low CRF concentration in toto. It is not possible to examine such an alternative directly in humans.

The findings of direct interest in this study seem to be the low 5-HIAA and CRF values related to the preference for carbohydrate. It is known from numerous experiments in animals that serotonin regulates carbohydrate intake (see reports in this supplement). The observations briefly summarized earlier indicate that this is also valid in humans, particularly in women with abdominal obesity. This in turn suggests an aberrant regulation of carbohydrate intake in such women, on the basis of an abnormality of serotonin concentrations in the brain. The closer nature of such an abnormality may be at the level of serotonin receptors in the brain. It seems possible to approach this problem further by using pharmacologic probes for these alternative possibilities.

Another question in this context is to try to understand whether the pathologic finding in CSF neuropeptide concentrations might be connected with the peripheral endocrine perturbations, particularly observed in visceral obesity. CRF has several functions in the brain, regulating not only corticotropin secretion but also the autonomic nervous system, as well as connections with several other control centers for peripheral endocrine and metabolic regulations. The closer connections here, if any, remain speculative, but may be accessible by further experimental studies using specific pharmacologic probes.

Serotonin agonists are currently used in the treatment of obesity. In animals, they have been shown to increase central concentrations of serotonin by either an increased secretion and/or a reuptake inhibition. The findings of low serotonin concentrations in CSF of obese women provide a more solid and logical basis for such therapy. It seems most likely that the mode of action in humans, as in experimental animals, is mediated via an elevation of low serotonin levels in brain centers, regulating in particular the carbohydrate intake.

Dexfenfluramine is a serotonin-release agonist with a component of reuptake inhibition. This drug has been demonstrated to be effective in the treatment of human obesity (see reports in this symposium). Furthermore, in

conditions in which appetite dysregulations are associated with various depressive and other mental symptoms, such as the premenstrual syndrome, dexfenfluramine has been shown to have beneficial effects on the whole syndrome, ie, not only the appetite dysregulation, but also the mental symptoms. Such findings indicate that the drug not only affects appetite regulation, but has more widespread central effects.

Findings suggesting that dexfenfluramine regulates peripheral endocrine secretions and nervous activities independently of its effect on appetite and energy intake are of particular interest. For example, blood pressure, as well as noradrenaline and renin concentrations, is decreased after dexfenfluramine administration, with unchanged energy intake fully controlled under metabolic ward conditions.[21] Furthermore, data suggesting that insulin resistance is improved by the compound in question have been reported.[22] Such observations suggest at least two interesting possibilities. First, dexfenfluramine might have other effects of at least equal clinical interest to the body weight decrease, namely to improve components of the metabolic syndrome. It seems of particular importance to explore these problems further, because additional direct effects on the complications of visceral obesity in particular would be highly desirable. An effective drug with such effects is currently not available and is much needed. Second, observations of direct effects on metabolic and blood pressure complications suggest that a low serotonin level in the brain may in fact be connected in some way to the metabolic and blood pressure abnormalities of obesity, which are improved by dexfenfluramine independently of body weight decrease.

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