Autonomic nervous control of white adipose tissue: studies on the role of the brain in body fat distribution
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CHAPTER 7

Hypothesis: HIV-associated adipose redistribution syndrome as a selective autonomic neuropathy


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Abnormal body-fat distribution in HIV-1-associated adipose redistribution syndrome (HARS) remains unexplained at present. White adipose tissue is controlled by humoral factors and by neural regulation. Sympathetic innervation stimulates lipolysis, whereas parasympathetic innervation has an anabolic influence on white adipose tissue. Results of neuroanatomical studies showed a clear somatotopy with respect to autonomic control of white adipose tissue by both the sympathetic and parasympathetic branch, with separate sets of autonomic neurons innervating either the subcutaneous or the visceral fat compartment. Thus, the CNS is likely to be a key player in regulation of body-fat distribution. We propose that HARS is mediated by effects of antiretroviral treatment on the CNS and could indicate a change in autonomic balance resulting in redistribution of adipose tissue.

Potent combination antiretroviral therapy for HIV-1 infection has resulted in striking reductions in associated morbidity and mortality. However, soon after the widespread introduction of such treatment, a novel lipodystrophy syndrome was reported in HIV-1-infected patients, which was characterised by insulin resistance, hypertriglyceridaemia, and abnormal distribution of adipose tissue. Many studies have since addressed the pathogenesis of this disorder, mainly focusing on pharmacologically induced mitochondrial toxic effects and altered adipocyte differentiation. However, the abnormal distribution of adipose tissue has remained unexplained. Here, we propose that this HIV-1-associated adipose redistribution syndrome (HARS) is mediated via the CNS and represents a selective neuropathy.
PART B DISCUSSION AND PERSPECTIVES

Background
Body-fat redistribution in HARS entails disproportional disposition of intra-abdominal adipose tissue and wasting of subcutaneous fat, especially in the extremities, buttocks, and face. Initially, the syndrome was solely linked to use of protease inhibitors, but the present idea is that both protease inhibitors and nucleoside reverse transcriptase inhibitors contribute to the syndrome, although in-vitro evidence is sparse for nucleoside reverse transcriptase inhibitors. HARS was initially reported to arise in more than half of HIV-1-positive patients treated with protease inhibitors with an average delay of 10 months, but a lower prevalence (17% after 18 months) has been reported.

Since visceral accumulation of white adipose tissue with peripheral fat wasting is a prominent feature of Cushing's syndrome, several studies have looked at the hypothalamus-pituitary-adrenal (HPA) axis in HIV-1-infected patients with antiretroviral-associated lipodystrophy. Yanovski and colleagues investigated this axis in patients with HARS, and reported that they had lower urine excretion of free cortisol and normal glucocorticoid receptor number and affinity compared with controls or patients with Cushing's syndrome. Therefore, hypercortisolism is unlikely to account for the noted phenotype, confirming initial reports of normal urine cortisol excretion and dexamethasone suppression in HARS. On the other hand, the serum cortisol/dehydroepiandrosterone ratio has been reported to be associated with clinical progression and atherogenic lipid alterations in HARS. However, the relevance of this ratio for fat redistribution is unclear at present. Alteration of tumour necrosis factor alpha homeostasis induced by combination antiretroviral therapy has been proposed as a risk factor for HARS development, but again is unlikely to account for fat redistribution. Alternative pathophysiological mechanisms have been the subject of intense research. Findings of in-vitro studies have shown protease inhibitors to affect fat-cell differentiation, and these observations have been extended to altered adipocyte differentiation markers in subcutaneous fat tissue of patients with HARS. Furthermore, results of several studies have shown nucleoside reverse transcriptase inhibitors to induce mitochondrial toxic effects, and dysfunction induced by these inhibitors has been proposed to be important in the metabolic changes in adipose tissue. However, these mechanisms offer no explanation whatsoever for adipose tissue being affected differently in distinct regions of the body—ie, for the redistribution of fat tissue characteristic of HARS.

Our group has shown novel neural pathways in rats between the CNS and white adipose tissue compartments with the retrograde transneuronal tracer pseudorabies virus. There seemed to be clear separation of central autonomic neurons projecting to either the subcutaneous or the intra-abdominal fat compartment. This pronounced somatotopy represents a plausible model to account for effects of hormones and phar-
macological agents on body fat distribution. White adipose tissue appeared to be innervated by parasympathetic input from the dorsal motor nucleus of the vagal nerve in the brainstem. Vagal motor neurons in this nucleus projecting to intra-abdominal fat pads were localised medially to neurons projecting to subcutaneous fat. Selective surgical lesions of this parasympathetic input resulted in striking local insulin resistance, with a 30% fall in glucose and fatty-acid uptake and a more than 50% rise in hormone-sensitive lipase activity. Thus, parasympathetic innervation of white adipose tissue enhances insulin sensitivity congruent with an anabolic function—ie, fat accumulation. Conversely, sympathetic stimulation of subcutaneous adipose tissue induces lipolysis and free fatty-acid mobilisation. The sympathetic motor neurons in the spinal cord, receiving input from sympathetic brainstem areas such as the A1 region, show a clear somatotopic organisation similar to parasympathetic outflow to the visceral and subcutaneous white adipose tissue compartments. Parasympathetic neurons in the dorsal motor nucleus of the vagal nerve receive innervation from at least four regions where the blood-brain barrier is absent for various hormones and nutrients, such as the hypothalamic arcuate nucleus and the area postrema. If antiretroviral drugs could reach these regions and have differential adverse effects on autonomic neurons in the CNS that project either to the visceral or to the subcutaneous white adipose tissue compartment, an imbalance in the autonomic control of subcutaneous and visceral fat tissue might ensue, and hence an aberrant distribution of adipose tissue, as seen in people with HARS.

We noted raised plasma norepinephrine concentrations in patients with HARS, providing circumstantial evidence for altered sympathetic input in this disorder. Indeed, diffuse autonomic dysfunction has been noted in HIV-1-infected patients, with more frequent and severe autonomic involvement in patients with AIDS. These findings, however, cannot account for the localised adipose tissue changes seen in HARS. Data suggest that a substantial number of antiretroviral agents, including protease inhibitors, penetrate the CNS, as shown by detectable concentrations in cerebrospinal fluid. Indinavir is easily detected in cerebrospinal fluid, and there have been reports of limited, but detectable, concentrations of amprenavir, saquinavir, and ritonavir. However, at present, the relation between concentrations of drugs in cerebrospinal fluid and tissue in the brain areas involved in our hypothesis (area postrema and arcuate nucleus) is unclear. The arcuate nucleus, in which the blood-brain barrier is absent for various compounds, is a potential target; it is essential in neuroendocrine feedback of leptin and insulin on the brain because it expresses leptin and insulin receptors and responds via intrahypothalamic neuropeptidergic pathways to the endocrine milieu. Selective damage to the arcuate nucleus of rats by means of peripherally injected monosodium glutamate in the neonatal period induces adiposity in the presence of hypophagia and signs of reduced sympathetic outflow from the hypothalamus. Moreover, leptin
administration to rats treated with monosodium glutamate fails to reduce the size of intra-abdominal fat depots compared with a pronounced reduction in intact rats. This finding might be explained in this model via damage to autonomic neural connections originating in the arcuate nucleus and innervating visceral white adipose tissue via multisynaptic pathways. Glutamate is assumed to have an important role in the pathogenesis of HIV-1-related central neurotoxic effects. Quantitative differences in limb fat loss between different treatment regimens, even within one particular class of antiretroviral drugs, might be associated with differences between the various drugs in blood-brain barrier passage, neurotoxic effects, or both.

**Hypothesis**

HARS is a disorder resulting from selective damage by antiretroviral drugs to autonomic pathways in the CNS, innervating either the subcutaneous or visceral fat depots. Specifically, increased sympathetic over parasympathetic tone of subcutaneous fat innervation induces selective loss of subcutaneous fat, and decreased sympathetic over parasympathetic tone of visceral fat innervation induces accumulation of intra-abdominal fat. The damage might be reversible (altered neuronal function) or irreversible (neuronal cell death).

**Testing the hypothesis**

For antiretroviral agents to affect autonomic neurons within the CNS they must enter the brain. Experiments in rats exposed to different combinations of antiretroviral drugs including protease inhibitors and nucleoside reverse transcriptase inhibitors should assess their penetration in dissected and homogenised hypothalamus and brainstem areas containing, respectively, the preautonomic and autonomic motor neurons. Furthermore, stereotaxic local administration of antiretroviral agents in the hypothalamus and brainstem should be followed by assessment of body fat distribution and metabolic variables, to confirm that these treatments induce the expected changes. Imaging techniques (MRI) and hyperinsulinaemic clamp studies will be needed to monitor body fat distribution and insulin sensitivity. Moreover, conventional morphometric techniques (Nissl staining in combination with computer-assisted image analysis) should indicate selective neuron loss or altered neuronal activity in the nuclei involved after systemic treatment and local administration. A combination of retrograde neuronal tracing (immunocytochemical detection of pseudorabies virus) from the subcutaneous and visceral fat depots, selective surgical lesioning of the vagal input, and morphometry of hypothalamic and brainstem nuclei should indicate if indeed depot-specific damage takes place during chronic antiretroviral treatment. Furthermore, the mechanism of the postulated selective damage by antiretroviral agents to either visceral or subcutaneous autonomic output should be assessed, focusing on differential receptor expression or
enzyme activities in these neuron sets. Predominant damage to autonomic innervation of only one adipose tissue compartment is a possibility and might accord with clinical observations of dissociations between subcutaneous fat wasting and abdominal fat gain. Finally, differential changes in autonomic innervation of lipoatrophic and lipogenetic compartments should be investigated in HIV-1-infected patients with HARS. One way to compare these compartments is by microdialysis of neurotransmitters and their metabolites in phenotypically distinct fat compartments. Comparison of subcutaneous thigh fat as a lipoatrophic compartment with visceral fat could, however, be hampered by ethical considerations about obtaining intra-abdominal fat biopsy specimens for research purposes. Dorsocervical fat accumulation might serve as an alternative for visceral fat, although the source of the autonomic innervation of this fat depot has not been established.

REFERENCES
PART B DISCUSSION AND PERSPECTIVES


