Hypothesis: Hypothalamic Dysfunction and Lipoatrophic Diabetes

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INTRODUCTION

The concept that the hypothalamus controls anterior pituitary function via the production of neurohormonal releasing and inhibitory factors (RFs and IFs, respectively) is well documented (1).

There is a growing body of evidence relating endocrine disorders to hypothalamic dysfunction that has resulted in a wide variety of endocrine and metabolic imbalances (2, 3). In an effort to explain the pathophysiologic expression of the bizarre clinical entity known as lipoatrophic diabetes (LD), we have attempted to correlate our laboratory findings with the current knowledge regarding hypothalamic-hypophyseal-target organ interactions.

Generalized or total lipoatrophic diabetes, relatively rare, has long been thought to be genetically determined. The onset of the disease is frequently heralded by fever. This disease is characterized by a loss of subcutaneous and other body fat, skeletal muscle overgrowth, bone overgrowth with advance maturation, hepatomegaly, splenomegaly, genital enlargement, hyperpigmentation of the skin with acanthosis nigricans, hyperlipemia, and insulin-resistant hyperglycemia.

Our more recent clinical data gives substantive chemical evidence that hypothalamic dysfunction may exist in patients with LD (4, 5) substantiating the early speculations of Seip in 1959 (6). Our patients had apparently normal circulating levels of pituitary hormones in the face of clinical evidence suggesting obvious excessive hormonal stimulation. Plasma from one of these patients who had been hypophysectomized in an effort to alleviate the metabolic and physical distortions of the disease, revealed comparable levels of releasing factors [corticotropin-releasing factor (CRF), follicle-stimulating hormone releasing factor (FRF), and melanocyte-stimulating hormone releasing factor (MRF)] both pre- and postoperatively. These data indicated that the pituitary in situ had no effect on the progression or amelioration of the disease and implicated hypothalamic involvement.

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Subsequent study of five patients with generalized lipodystrophy has established the presence in the plasma, of detectable releasing-factor activity as a consistent finding in association with the other symptoms of this disease (4, 5).

The demonstration of releasing-factor activity in the plasma of these patients was unexpected in view of the demonstrated absence of such activity in the intact human (7). Animal studies have demonstrated that detectable levels of releasing factor (FRF and CRF) are present in the peripheral plasma of hypophysectomized preparations (8, 9). Corbin et al. (7) corroborated and extended these findings by demonstrating the presence of levels of follicle-stimulating hormone releasing factor (FRF) and luteinizing hormone releasing factor (LRF) activities in the plasma of a hypophysectomized human. Studies on the “internal” feedback phenomenon [the ability of an anterior pituitary hormone to effect, by itself, and in the absence of peripheral target organ hormone intervention, its respective hypothalamic releasing factor (RF) and inhibiting factor (IF)] in animals (8, 10), prompted us to speculate whether such a mechanism existed in humans. The lipodystrophic patients appeared as functionally hypophysectomized and we administered corticotropin (ACTH) in an effort to simulate the internal feedback (5, 11). A significant reduction in plasma CRF activity was observed in three out of four LD patients. The normal control showed no detectable level of CRF before or after ACTH. It remained an enigma that exogenous hormones could eliminate the RF in most LD patients but that the endogenous levels of corticotropin present were ineffective.

PATHOPHYSIOLOGY

1. Feedback

Originally it was thought that the muscle and bone overgrowth and the hyperpigmentation were due to hypersecretion of growth hormone and melanocyte-stimulating hormone (MSH), respectively. Since the releasing factors have been implicated in the biosynthesis of pituitary hormones (12–14), it was possible that structural variants of pituitary hormones were produced, resulting in the clinical pathophysiology observed. These hormonal variants themselves may not possess any inhibitory feedback effects. However, the persistence of this disease entity in the hypophysectomized patient precluded hypophyseal involvement (15). If the syndrome had been ameliorated by the hypophysectomy, it would have been tempting to speculate further that the refractoriness of the hypothalamus to regulation by the hypophyseal–target organ axis, led to releasing factor hypersecretion. On the other hand, one can speculate that the RFs may be secondary to a generalized hypothalamic derangement with the actual metabolic defect residing at the receptor site levels of the various tissues (fat, muscle, bone, skin) where the disease is manifested.

2. Hypothalamic Biogenic Amines

There is a growing body of evidence that implicates multiple monoaminergic neuronal systems in the control of the secretion of most, if not all, of the hormones secreted by the pituitary gland. Modification of the synthesis, release, or metabolism of brain catecholamines has been shown to interfere with secretion of anterior pituitary hormones (16–18).

Norepinephrine, dopamine, and serotonin appear to be transmitters at synaptic junctions in the basal medial hypothalamus regulating the secretion of the hypo-
physiotropic hormones (RFs and IFs) which in turn regulate the secretion of the pituitary hormones (19). Our discussion will be confined to norepinephrine and dopamine because of the scanty evidence concerning the role of serotonin and its relative importance to this control system.

Relatively large amounts of norepinephrine and dopamine are stored in the median eminence as demonstrated by chemical assays (20, 21). Morphological studies have shown that discrete populations of neurons which contain these monoamines end in the hypothalamus (22). The generalized scheme describing the interconnections between catecholamine neurons and RF/IF neurons with the physiotropic area is presented in Fig. 1. L-dopa in man (23–26) can stimulate the release of CRF, prolactin-inhibiting factor, FRF, and LRF. Since L-dopa is decarboxylated to dopamine and thence to norepinephrine by the action of dopamine-β-hydroxylase, it is possible that either dopamine or norepinephrine or both may subserve the hypothalamic RF/IF mechanism.

Fluctuations of norepinephrine content occur in certain states of altered endocrine balance, e.g., turnover of norepinephrine increases after adrenalectomy but decreases after hypophysectomy (27, 28). Data supplied mainly by Ganong (29) has supported the existence of a central noradrenergic system that inhibits ACTH secretion. The inhibitory role of norepinephrine neurons is strengthened by experimental results indicating that rises in tonic corticosterone secretion increase after lesions of ascending norepinephrine pathways (30).

Further results obtained by systemic treatment with such drugs as dopa, amphetamine, chlorpromazine, and reserpine clearly suggest an inhibitory role for the norepinephrine system (31, 32).

Many studies support the conclusion that releasing and inhibiting factors are present in the basal medial hypothalamus (hypophysiotropic area), that they are

Fig. 1. Generalized scheme describing interconnections between catecholamine-producing and RF/IF-producing neurons within the hypothalamus. (MAM = mamillary body; OC = optic chiasma; AL = anterior hypophyseal lobe; PL = posterior hypophyseal lobe; ME = median eminence; RF/IF = releasing factor/inhibitory factor; CA = catecholamine)
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present in portal blood and that dopamine induces discharge of these substances from neurosecretory elements of the hypothalamus (33).

In view of these data suggesting inhibition by norepinephrine and stimulation by dopamine, it is tempting to speculate that in the LD patient, lowered norepinephrine secretion and dopamine excess resulted in constant elevated secretion of releasing factors.

3. Metabolic Considerations

One of the more consistent features of LD is the presence of insulin resistance and is remarkable because the resultant hyperglycemia rarely leads to ketosis. It is important to note in this context that the hypophysiotropic area exerts an important regulatory effect on glucose homeostasis and contains within its functional boundaries the hypothalamic loci involved in the control of insulin release (34) and lipid metabolism (35). Largely from the work of Frohman (36) it has been demonstrated that the hypothalamic control is dual in nature, involving both the sympathetic and parasympathetic components of the autonomic nervous system. The ventromedial nucleus and the ventrolateral hypothalamus represent the origin of circuits that directly innervate the liver via the sympathetic and parasympathetic outflow systems, respectively.

It is also possible that a defective adenyl cyclase system is present in the LD such as has been postulated by Cerasi and Luft for diabetes mellitus (37). Reduced tissue sensitivity to insulin or an increased sensitivity to or excess production of catecholamines results in the metabolic derangements. A defective adenyl cyclase system could explain the lack of response of the pituitary to the excessive production of RF. Again, this insensitivity to endogenous RF would implicate extrapituitary effects of the RFs.

Whatever the mechanisms involved there can be little doubt that the work of Frohman lays the foundation for a direct correlation between the presence of the hypothalamic disorder and the presenting diabetic symptoms.

THERAPEUTIC IMPLICATIONS

Within this theoretical framework, we attempted manipulation of the hypothalamic hypophysiotropic mechanism by pharmacological blockade of dopamine. It would follow that drugs which increase the “tone” of the adrenergic systems (either through increased catecholamine secretion or direct stimulation of adrenergic receptors) may lead to increased output of hypophysiotropic factors; conversely, agents which dampen the adrenergic system may lead to attenuation or inhibition of the RF mechanism.

Table 1 is a compilation of various classes of pharmacological agents which can affect the adrenergic (dopamine and norepinephrine) mechanism, through biosynthetic pathways (preloading with precursors or inhibition of transforming enzymes) or through direct effects on nerve terminal receptors (receptor inhibition and stimulation, displacement and/or depletion of native neurotransmitters or direct destruction of the terminals themselves).

The work of Sherman and Kolodny (38) and Kolodny et al. (39), has supported the hypothesis that chronic hypersecretion of growth hormone in certain cases of acromegaly and gigantism is nonautonomous and is due to hypothalamic dysfunction. They demonstrated that drugs interfering with catecholamine output, such as chlorpromazine, were effective in markedly lowering growth hormone concentra-
TABLE 1
MAJOR EFFECTS OF DRUGS ON BRAIN DOPAMINE (DA) AND NOREPINEPHRINE (NE)

| Drug | Effect |
|------|--------|
| Pimozide | Selective blocker of DA receptors |
| Fluspirilenol | (diphenylbutylpiperidines) |
| Aponorphine | Short-acting DA receptor-stimulating agent |
| ET 495 | |
| α-Methyldopa hydrazine | Blocks conversion of levodopa to dopamine only within peripheral tissues |
| α-Methyltyrosine | Inhibits tyrosine hydroxylase and leads to eventual decrease of dopamine and NE |
| α-Methyldopa (Aldomet) | Produces α-methyl DA and α-methyl NE which act as false transmitters and displace DA and NE |
| Disulfiram | Inhibit dopamine-β-hydroxylase which prevents transformation of DA to NE |
| DDC (diethylthiocarbamate) | |
| FLA-63 | |
| Phentolamine | α-Adrenergic blocker |
| Propranolol, Pronethalol, Pindolol | β-Adrenergic blocker |
| DOPS (dihydroxyphenylserine) | Increases NE synthesis (DOPS is precursor for NE) |
| Reserpine | Depletion of DA and NE |
| Pargyline, Tranylepromine, Nialamide | MAO inhibitors—raise DA and NE |
| Imipramine, Amitriptyline (tricyclic antidepressives) | Inhibit uptake of DA and NE |
| L-Dopa | Increase DA and NE |
| 6-OH Dopamine | Depletes and destroys NE terminals |
| Guanethidine | Depletes NE terminals (peripheral tissue) |
| Spiroperidol | Block DA receptors, small effect on NE receptors |
| Haloperidol | (butyrophenones) |
| Methylperidol | |
| Fluphenazine | Block DA receptors, small effect on NE receptors |
| Perphenazine | (phenothiazines) |
| Clopenthixol | Block DA receptors, small effect on NE receptors |
| Flupenthixol | (thioxanthenes) |
| Clozapine (dibenzepine) | Blocks both DA and NE receptors |
| Phenoxymethylamine | Blocks NE receptors |
| Thioridazine, Chlorprothixine, | Weak and equal blockers of DA and NE receptors |
| Pipamperone, Chlorpromazine | |

...tions and eliminating the headaches and visual disturbances of an acromegalic patient.

Since chlorpromazine was presumably acting through its central nervous system antiadrenergic effect, this drug (100 mg/day) was administered to our lipodystrophic patients and control subjects over 21 days. The initial response to the drug was a reduction in the levels of releasing factors followed by a subsequent return of both CRF and FRF to levels seen before drug administration. The normal patients initially had no detectable level of RF, although after 21 days of therapy, CRF and not FRF levels were detectable. It was, therefore, impossible for us to...
decide whether the CRF levels shown in the LD patients after 3 weeks were due to the disease state or to the effects of the drug; very likely both factors contributed. The picture with FRF appears clearer. The increasing level of FRF activity towards preexisting values is interpreted as a reflection of the hypothalamic dysfunction overriding the apparent drug effect. On the basis of our findings, chlorpromazine did not appear to be the drug of choice.

**Hypothesis**

Figure 2 depicts the normal conversion pathway of tyrosine to dopamine and norepinephrine in the brain and its effect on the neurosecretory cell at the level of the hypothalamus. On the basis of our data showing a constant release of hypophysiotropic hormones in the lipatrophenydependent diabetes syndrome, the problem is presumed to be hypothalamic in origin. There may exist a genetically transferred inborn error in metabolism that inhibits the normal metabolism of tyrosine in the brain. This defect may possibly exist as a lack of dopamine-β-hydroxylase, the enzyme necessary to convert dopamine to norepinephrine. When insufficient amounts of norepinephrine are present, the normal inhibition of the releasing factors is removed and constant uncontrolled stimulation of the releasing factors by excessive amounts of dopamine results.

It is noteworthy that the lipatrophenydependent diabetes syndrome persisted in the single patient who had been hypophysectomized. Moreover, the continued presence of pigmentation in this patient would indicate that hypophyseal MSH was not involved. It is tempting to speculate that excess dopa was present and was eventually metabolized to dopa-melanin in the skin (40). An interesting but speculative correlation arises from this suggestion: the activity of tyrosinase, the enzyme which converts tyrosine to L-dopa, and also L-dopa to dopaquinone which is eventually metabolized to dopa-melanin, is temperature dependent. Increased temperature accelerates the tyrosinase reaction and might account for the excess dopa and its subsequent metabolism to dopa-melanin, resulting in the increased pigmentation.

![Diagram](https://example.com/diagram.png)

**Fig. 2.** Schematic representation of the metabolism of tyrosine in the brain and the relationship to hypophysiotropic hormones. Sites of action of various drugs are indicated at various steps. (FLA-63 = bis (4-methyl-1-homopiperazinyl-thiocarbonyl) disulfide; ET 495 = 7-(2"-pyrimidyl-4-1 piperonyl-piperazine); DDC = diethylthiocarbamate; DOPS = dihydroxyphenylserine; ME = median eminence; RF/IF = releasing factor/inhibitory factor)
seen in the body folds and in skin chronically exposed to heat sources. As infants, and recently, these patients have experienced bouts of abnormal hyperthermia, which may have been harbingers and perpetrators of the eventual hypothalamic dysfunction.

A further extension of the excess dopamine hypothesis may be based on the recent findings of Weinshilboum and Axelrod (41) and Fuxe et al. (42), who demonstrated that dopamine-β-hydroxylase increases in the blood of rats after hypophysectomy. Since hypophysectomy (as well as LD) leads to increased levels of releasing factors in the peripheral circulation and since dopamine appears to be the major neurotransmitter subserving the hypothalamic–hypophysiotropic hormone mechanism, the rise in dopamine-β-hydroxylase may represent a compensatory response to the absence of all feedback input. It can only be conjectured at this time that the increased dopamine-β-hydroxylase may be an attempt to convert excessive dopamine to norepinephrine, thus reducing the “drive” to the releasing factor mechanism. However, one may argue against this concept, since the untreated lipoatrophic diabetes patient (whether hypophysectomized or not) possesses persistent blood RF activities and this fact necessitates that we postulate a defect at the rate-limiting step (dopamine-β-hydroxylase) in the conversion of dopamine to norepinephrine.

The constant secretion of releasing factor is not affected by an internal feedback control and the levels of circulating pituitary hormones appear normal. This observation might be explained by increased catabolism of the pituitary hormones, although we have no data to support this assumption. The bizarre effects on lipid metabolism may be due to the excessive release of lipid-mobilizing factor which may also be controlled by hypothalamic neurons (43).

The pathological modification of brain catecholamines is expressed as RF hypersecretion as one component and certainly can affect other parameters, e.g., insulin levels, lipid mobilization, glucose metabolism. Since the collective evidence underscores the important and unique role of dopamine in regulating the hypothalamic–endocrine axis, it would follow that selective inhibitors of this catecholamine may be useful in the treatment of hypothalamically based diseases and hopefully will ameliorate the symptoms of this bizarre, disfiguring, and inevitably fatal disease. Data derived from our recent animal and clinical LD studies, employing Pimozide, a dopamine receptor blocker, tentatively support this hypothesis.

**SUMMARY**

The hypothesis is proposed that:

1. Lipoatrophic diabetes appears to possess a hypothalamic component, perhaps involving a genetically transferred defect in the enzyme, dopamine-β-hydroxylase.
2. Absence of normal inhibition by norepinephrine and unchecked stimulation by excess dopamine may be the cause of autonomous RF hypersecretion.
3. Internal feedback control appears nonexistent.
4. Hyperpigmentation cannot be due to MSH, since skin darkening persists after hypophysectomy. Dopa-melanin may account for the hyperpigmentation.
5. The persistence of the disease in the absence of the pituitary implicates an extrapituitary effect by releasing factors. Increased blood RF’s may be secondary to a generalized hypothalamic derangement with the actual metabolic defect residing at the receptor site of the various tissues (fat, muscle, bone, skin) where the disease is manifested.
6. Dopamine receptor blockers that block the effect of this neurotransmitter in the hypothalamus at the level of the neurosecretory cell, inhibitors of dopamine synthesis or stimulators of norepinephrine synthesis, should ameliorate the symptoms of this bizarre and disfiguring disease.

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