Functional Medicine University’s
Functional Diagnostic Medicine Training Program

Module 7 * FMDT 561C

Physiology of the Hypothalamus and Pituitary Gland
(Diseases of the Pituitary)
(Ectopic Hormone Production/Tumor Markers)

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Required reading: Increased 5-Lipoxygenase Immunoreactivity in the Hippocampus of Patients with Alzheimer’s disease. This article can be found in the download library on www.FunctionalMedicineUniversity.com
The Hypothalamus

As stated in a prior lesson, the hypothalamus is involved in the mediation of endocrine, autonomic and behavioral functions. The hypothalamus controls the release of hormones from the pituitary, and is involved with temperature regulation, food and water intake, sexual behavior, reproduction, control of daily cycles in behavior (circadian rhythms) and physiological states, and emotional responses.

The hypothalamus:

- coordinates drive-related activities that include hormonal, emotional and autonomic
- is connected to the limbic system (emotional)
- has outputs to the anterior and posterior lobes of the pituitary (hormonal)
- has connections to visceral and somatic nuclei of the brainstem and spinal cord (autonomic)

The hypothalamus is said to be neurologically ‘wired’ with other structures of the brain. This ‘wiring’ allows the hypothalamus to elicit specific metabolic, autonomic, hormonal and behavioral changes. The hypothalamus may indeed be the area of the” mind-body connection”, due to the fact that it elicits the previously mentioned specific changes, and acts like an integrative center for thoughts, emotion, memories and visceral functions. The influence of mediation, biofeedback and light therapy in treating certain conditions may have its basis on affecting the hypothalamus in a positive way. It is known that optic nerve stimulation (light) can stimulate the suprachiasmatic nucleus (SCN) of the hypothalamus, and that the neurons of the SCN are involved with circadian rhythms.

[Note: Light therapy (aka phototherapy) has been used to treat the following conditions: seasonal affective disorder (SAD), obsessive-compulsive disorders, jet-lag, sleep disorders, and attention-deficit/hyperactivity disorder (ADHD)]

Functional Anatomy of the Hypothalamus and the Pituitary Gland

The pituitary gland, also known as the hypophysis, has two distinct parts called the adenohypophysis (anterior pituitary) and the neurohypophysis (posterior pituitary). The pituitary is connected to the hypothalamus by the hypophysial stalk and lies in the sella turcica of the skull. There is an extensive network of vascular connections between the anterior pituitary and the hypothalamus. Blood flows from the hypothalamus through the hypothalamic-hypophysial portal vessels to the anterior pituitary.
Functional Medicine University’s  
Functional Diagnostic Medicine Training Program  
Module 7: FDMT 561C Physiology of the Hypothalamus and Pituitary Gland (Diseases of the Pituitary)  
(Ectopic Hormone Production/Tumor Markers)

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Hypothalamic Releasing and Inhibitory Hormones (Control of the Anterior Pituitary)

<table>
<thead>
<tr>
<th>Hypothalamic Hormones</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyrotropin-releasing hormone (TRH)</td>
<td>Stimulates secretion of TSH</td>
</tr>
<tr>
<td>Gonadotropin-releasing hormone (GnRH)</td>
<td>Stimulates secretion of FSH and LH</td>
</tr>
<tr>
<td>Corticotrophin-releasing hormone (CRH)</td>
<td>Stimulates secretion of ACTH</td>
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<tr>
<td>Growth hormone-releasing hormone (GHRH)</td>
<td>Stimulates secretion of growth hormone (GH)</td>
</tr>
<tr>
<td>Growth hormone-inhibitory hormone (somatostatin)</td>
<td>Inhibits secretion of GH</td>
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<tr>
<td>Prolactin-inhibiting hormone (PIH)</td>
<td>Inhibits secretion of prolactin</td>
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Hormones of the Anterior Pituitary

<table>
<thead>
<tr>
<th>Anterior Pituitary Hormones</th>
<th>Effect</th>
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</thead>
<tbody>
<tr>
<td>Growth hormone (GH) (somatotropin)</td>
<td>Stimulates body growth, lipolysis and secretion of Insulin-like growth factor-1; inhibits action of insulin on carbohydrate and lipid metabolism</td>
</tr>
<tr>
<td>Adrenocorticotropic hormone (ACTH)</td>
<td>Stimulates production of glucocorticoids(mainly cortisol) and androgens by the adrenal cortex</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (TSH)</td>
<td>Stimulates production of thyroid hormones</td>
</tr>
</tbody>
</table>
| Follicle-stimulating hormone (FSH)        | Stimulates development of the ovarian follicle  
Regulates spermatogenesis in the testis                                                                 |
| Luteinizing hormone (LH)                  | Causes ovulation and formation of the corpus luteum in the ovary  
Stimulates production of estrogen and progesterone by the ovary  
Stimulates testosterone production by the testes                                                      |
| Prolactin (PRL)                           | Stimulates milk production and secretion                                                                   |

Growth Hormone-Insulin-Liver Connection

Growth hormone’s metabolic effects, aside from causing growth, include:

- Increases the rate of protein synthesis
- Increases mobilization of fatty acids from the adipose tissue (fatty acids to acetyl-CoA)
- Increases fatty acid metabolism for energy production
- Decreases the rate of carbohydrate utilization
Adequate insulin and carbohydrates are needed to promote the action of growth hormone. Growth hormone causes the liver (mainly) to form proteins called somatomedin. The most commonly tested somatomedin is somatomedin C, which is used to identify patients with growth hormone deficiency, pituitary insufficiency and acromegaly. Somatomedin C has a major effect on cartilage and is also known as “insulin-like growth factor”. (Many of the somatomedin effects on growth are similar to the effects of insulin on growth and hence, its alternate name).

A hormone called ghrelin, produced mainly by the stomach, and to a lesser extent in the small intestine and elsewhere, has at least two major biological functions. The first is to stimulate growth hormone secretion and the second is to regulate energy balance by affecting the hypothalamus. From a functional medicine perspective, restoring gastrointestinal function may affect growth hormone secretion and energy regulation. There is definitely a brain-gut connection as most of you know. It is also interesting to note that exercise causes an increase in growth hormone secretion, which can then stimulate bone and cartilage growth.

**The Hypothalamus and the Posterior Pituitary**

The posterior pituitary acts as a supporting structure for nerve fibers that originate in the hypothalamus. The nerve endings in the posterior pituitary secrete two hormones; antidiuretic hormone (ADH), also known as vasopressin, and oxytocin. Both of these hormones are formed in the nuclei of the hypothalamus. The major target of ADH is the kidney, where its action is the conservation of body water. Oxytocin causes contraction of the pregnant uterus and aids in milk ejection by the breasts. Males also secrete oxytocin in the same area of the hypothalamus and in the testes. Pulses of oxytocin can be detected during ejaculation. It has been suggested that oxytocin may be involved in facilitating sperm transport due to its presence in seminal fluid.

**Disorders of the Hypothalamus and the Pituitary Gland**

Diseases of the endocrine glands typically cause hormone deficiencies or excesses. Hormone deficiencies are usually caused by damage to the endocrine gland, dysfunctional glands or congenital conditions. Excessive hormone secretion is usually due to tumors (benign or malignant), hyperplasia of the gland or by ectopic secretion by other tumors. (Tumors of non-endocrine tissues are capable of the production of ectopic hormones. An example of ectopic hormone production is oat cell carcinoma of the lung, which produces ectopic adrenocorticotropic [ACTH]).
Tumor Markers

- Tumor markers include a group of hormones, oncofetal proteins, enzymes and tumor antigens measured primarily in the blood, and sometimes in urine.
- Tumor markers are not in themselves specific enough to permit a diagnosis of malignancy to be made, but once a malignancy has been diagnosed and shown to be associated with elevated levels of tumor marker, the marker can be used to assess response to treatment.

Hormones
- ACTH (Adrenocorticotropic Hormone)
- Ectopic-ACTH
- Calcitonin (Thyrocalcitonin)
- HCG (Human Chorionic Gonadotripin)
- Parathyroid Hormone
- Prolactin

Oncofetal Antigens
- AFP (Alpha-Fetoprotein)
- CEA (Carcinoembryonic Antigen)

Enzymes
- ALT
- Alkaline Phosphatase
- Acid Phosphatase (Prostatic Acid Phosphatase [PAP])
- AST
- LDH (Lactic Dehydrogenase)
- PHI (Phosphohexose isomerase)

Tumor Associated Proteins
- CA 15-3 PSA (Prostate-Specific Antigen)
- CA 19-9 SCCA (Squamous Cell Carcinoma Antigen)
- CA 27.29
- CA 125

Other
- Beta₂ (B₂) – Microglobulin
- Serum Calcium
Adrenocorticotropic Hormone (ACTH, Corticotropin)

**Normal Findings**

AM: <80 pg/mL PM: <50 pg/mL

**Indications:**

The serum ACTH study is a test of anterior pituitary gland function that affords the greatest insight into the causes of either Cushing syndrome (overproduction of cortisol) or Addison disease (underproduction of cortisol)

**Test Results & Clinical Significance**

↑ Levels

- Addison disease
- Cushing disease
- Ectopic ACTH syndrome
- Stress: *ACTH is overproduced as a result of neoplastic overproduction of ACTH in the pituitary or elsewhere in the body by an ACTH-producing cancer. Stress is a potent stimulus to ACTH production.*

**Test Explanation:**

- An elaborate feedback mechanism for cortisol coordinates the function of the hypothalamus, pituitary gland, and adrenal glands.

- In the patient with Cushing syndrome an elevated ACTH level can be caused by a pituitary ACTH-producing tumor or a nonpituitary (ectopic) ACTH-producing tumor, usually in the lung, pancreas, thymus, or ovary. ACTH levels greater than 200 pg/mL usually indicate ectopic ACTH production. If the ACTH level is below normal in a patient with Cushing syndrome, an adrenal adenoma or carcinoma is probably the cause of the hyperfunction.

- In patients with Addison disease an elevated ACTH level indicates primary adrenal gland failure, as in adrenal gland destruction cause by infection, hemorrhage, or autoimmunity.
Calcitonin (Human Calcitonin [HCT], Thyrocalcitonin)

Normal Findings

Males:  ≤19 pg/mL       Females:  ≤14 pg/mL

Indications

This test is usually indicated to evaluate persons with suspected medullary carcinoma of the thyroid. Calcitonin is useful in monitoring response to therapy and predicting recurrences of medullary thyroid cancer. It is also useful as a screening test for those with a family history of medullary cancer.

Test Results & Clinical Significance

↑ Levels
- Medullary carcinoma of thyroid - Primary hyperparathyroidism
- C-cell hyperplasia - Secondary hyperparathyroidism
- Oat cell carcinoma of lung - Pernicious Anemia
- Breast carcinoma - Thyroiditis
- Pancreatic cancer: these cancers can act as an autonomous ectopic site of calcitonin production.

Test explanation:

Calcitonin is a hormone secreted by the parafollicular or C cells of the thyroid gland. Secretion is stimulated by elevated serum calcium levels. Calcitonin contributes to calcium homeostasis. It decreases serum calcium levels by inhibiting bone resorption and increasing calcium excretion by the kidneys.
Human Chorionic Gonadotropin \{HCG\}, Beta Subunit

**Normal Findings**

Qualitative: negative: positive in pregnancy  
Beta subunit: depends on the method & test used.

**Indications**

This test is used to diagnose pregnancy. It is also helpful in the monitoring of ‘high-risk’ pregnancies. It can also be used as a tumor marker for certain cancers. (trophoblastic)

**Test Results & Clinical Significance**

↑ Levels

- Pregnancy
- Ectopic Pregnancy:
  - *Highest beta HCG levels (,30,000 milli-international units/mL) are recorded in pregnancy.
  - *Lowest amounts are generally seen in ectopic pregnancy.*
- Hydatidiform mole of uterus
- Choriocarcinoma of uterus
- Germ cell (choriocarcinoma, teratomas, embryonal cell) tumors of testes or ovaries
- Other tumors (poorly differentiated tumors, such as hematoma and lymphoma.

**Test explanation**

Ectopic pregnancy, hydatidiform mole of the uterus, and choriocarcinoma of the uterus can all produce HCG. Germ cell tumors (choriocarcinoma, embryonal cell cancers) of the testes or ovaries can produce HCG in men and nonpregnant women, respectively. Primary liver cell cancers (hepatoma) can also make HCG. In these tumors, HCG is used as a valuable tumor marker to aid in tumor identification. For example, HCG is serially measured in patients with cirrhosis, because they have a high chance of developing a hepatoma. If detected early enough, the tumor can be removed and the patient cured. HCG is also used to monitor the therapy and disease progression and/or the regression of these tumors.
Parathyroid Hormone (PTH, Parathormone)

**Indications**

PTH is measured to assist in the evaluation of hypercalcemia or hypocalcemia. It is routinely monitored in patients with chronic renal failure (CRF).

**Test Results & Clinical Significance**

**↑ Levels**
- Hyperparathyroidism secondary to adenoma or carcinoma of the parathyroid gland.
- Non-PTH-producing tumors (paraneoplastic syndrome) commonly noted with lung, kidney, or breast carcinoma (These tumors produce a ‘PTH-related protein’ that acts like PTH.)

**↓ Levels**
- Hypercalcemia
- Metastatic bone tumor
- Hypercalcemia of malignancy (most often with lung, breast, or lymphoma cancer)
- Sarcoidosis: These patients can develop elevated serum calcium levels, thus reducing PTH.

**Test Explanation:**

- PTH is the only hormone secreted by the parathyroid gland in response to hypocalcemia. PTH is one of the major factors affecting calcium metabolism.
- Primary hyperparathyroidism is most often caused by a parathyroid adenoma and only rarely from parathyroid cancer. These patients have high PTH and calcium levels.
Prolactin Level (PRL)

Normal Findings

Adult male: 0-20 ng/mL
Adult female: 0-25 ng/mL  Pregnant female: 20-400 ng/mL

Indications

Prolactin levels are used to diagnose and monitor prolactin-secreting pituitary adenomas.

Test Results & Clinical Significance

↑ Levels

- Galactorrhea
- Amenorrhea: Patients who have had normal menses and then stop having menses may be found to have elevated prolactin levels. Many are subsequently found to have prolactin-secreting pituitary adenomas.
- Prolactin-secreting pituitary tumor
- Metastatic cancer of pituitary gland
- Hypothyroidism
- Paraneoplastic syndrome: Associated with ectopic production of prolactin
- Stress
- Polycystic ovary syndrome

Test explanation

Prolactin is a hormone secreted by the anterior pituitary gland (adenohypophysis). In females, prolactin promotes lactation.
Alpha-Fetoprotein (AFP, Alpha-Fetoprotein)

**Normal Findings**

- Adult: <40 ng/mL or <40 mg/L (SI units)
- Child younger than 1 year: <30 ng/mL
- Ranges are stratified by weeks of gestation and vary among laboratories

**Indications**

This test is used as a screening marker indicating increased risk for birth defects, such as fetal body wall defects, neural tube defects, and chromosomal abnormalities. It can also be used as a tumor marker to identify cancers.

**Test Results & Clinical Significance**

↑ Non maternal Serum Levels
- Primary hepatocellular cancer (hepatoma)
- Germ cell or yolk sac cancer of the ovary
- Embryonal cell or germ cell tumor of the testes

**Test explanation**

- Alpha-fetoprotein (AFP) is an oncofetal protein normally produced by the fetal liver and yolk sac. It is the dominant fetal serum protein in the first trimester of life and diminishes to very low levels by the age of 1 year. Normally it is found in very low levels in the adult.

- AFP is also used as a tumor marker. Increased serum levels of AFP are found in as many as 90% of patients with hepatomas.

- Other cancers (e.g., stomach, colon, lung, breast, lymphoma)
  - Liver cell necrosis (e.g., cirrhosis, hepatitis)
  - Cancers contain undifferentiated cells that may carry the surface markers of their fetal predecessors.
Carcinoembryonic Antigen (CEA)

Values for CEA (Measured in ng/mL)

- 0 – 5 → Non-malignant
- 5 – 10 → Equivocal
- 10 – 20 → Suggests tumor or following a resection of poor prognosis
- 20 – 50 → Malignant disease

Test explanation

CEA is a protein that normally occurs in fetal gut tissue. This tumor marker has been found in patients who have a variety of carcinomas (e.g., breast, pancreatic, gastric, hepatobiliary), sarcomas, and even many benign diseases (e.g., ulcerative colitis, diverticulitis, cirrhosis). Chronic smokers also have elevated CEA levels.

Acid Phosphatase (Prostatic Acid Phosphatase [PAP])

Normal Findings

- Adult/elderly: 0.13 – 0.63 units/L
- Child: 8.6 – 12.6 units/mL
- Newborn: 10.4 – 16.4 units/mL

Indications

Total acid phosphatase and specifically the PAP isoenzyme is primarily used to stage prostatic carcinoma and to monitor the efficacy of treatment.

Test Results & Clinical Significance

↑ Levels
- Prostatic carcinoma
- Benign prostatic hypertrophy
- Prostatitis
- Multiple myeloma
- Thrombocytosis
- Lysosomal disorders
- Renal diseases
- Liver diseases, such as cirrhosis
Test explanation

Acid Phosphatase (Prostatic Acid Phosphatase [PAP])

Usually (but not always) elevated levels are seen in patients with prostatic cancer that has metastasized beyond the capsule to other parts of the body, especially bone. Since PAP is not elevated in early stage prostate disease, this test is not recommended for screening.

Phosphohexose Isomerase (PHI): (enzyme found in muscle used for glucose metabolism)

Diseases of the heart, liver, skeletal muscles as well as certain malignancies, (especially carcinoma of the breast, prostate, and intestines) may cause an elevation of serum PHI. It is thought in active cancer the elevation may be due to liver or bone metastasis. Although PHI may be elevated from several different causes it is useful as a screening device to establish the presence or absence of certain types of cancer as well as progress of treatment.

Squamous Cell Carcinoma Antigen

SCCA has been shown to be elevated with squamous cell carcinoma of the cervix, and in squamous cell carcinomas of the lung, pharynx, larynx, palate, tongue, and neck.

Alanine Aminotransferase (ALT or SGPT)

A specific liver enzyme found increased in hepatitis, liver metastasis, obstructive jaundice, hepatic congestion, and infectious mononucleosis. ALT is decreased in pyridoxine deficiency.

Aspartate Aminotransferase (AST or SGOT)

Found elevated in hepatic disease, muscle damage, pancreatitis, and neoplasia. It is found decreased in pyridoxine deficiency and terminal stages of liver cancer.
Lactic Dehydrogenase (LDH)

Normal Findings

Isoenzymes

Adult/elderly:
- LDH-1 17% to 27% - Heart and RBCs
- LDH-2 27% to 37% - WBCs
- LDH-3 18% to 25% - Lungs
- LDH-4 3% to 8% - Kidneys, Placenta, Pancreas
- LDH-5 0% to 5% - Liver and skeletal muscle

Indications

This is an intracellular enzyme used to support the diagnosis of injury or disease involving the heart, liver, RBC’s, kidneys, skeletal muscle, brain, and lungs.

Test Results & Clinical Significance

↑ Levels
- MI - Skeletal muscle disease and injury
- Pulmonary disease - Renal parenchyma disease
- Hepatic disease - Neoplastic states
- RBC disease - Lymphoma & other reticuloendothelial system tumors
- Pancreatitis - Advanced solid tumor malignancies

Test Explanation

The enzyme LDH is found in the cells of many body tissues, especially the heart, liver, RBCs, kidneys, skeletal muscle, brain, and lungs. LDH is the enzyme that is involved in the catalytic conversion of pyruvate to lactate.

Clinical Priorities

Because LDH is widely distributed throughout the body, the total LDH level is not a specific indicator of any disease or organ injury. Isoenzymes are more specific and helpful diagnostically. When LDH-1 is greater than LDH-2, myocardial injury is strongly suspected. Isolated elevations of LDH-5 usually indicate hepatocellular injury or disease.

LDH optimal ranges are 140 to 200 units per liter. A common finding in reactive hypoglycemia is a decreased fasting blood glucose along with a decreased LDH (<140).
CA 27.29 and CA 15-3 Tumor Marker  (CA = Cancer Antigen)

**Normal Findings**

CA 27.29: <38 units/mL  CA 15-3: <22 units/mL

**Indications**

The CA 15-3 and CA 27.29 antigens are tumor-associated serum markers available for breast cancer monitoring.

**Test Results & Clinical Significance**

↑ Levels

Metastatic breast cancer

**Test explanation**

Carcinoembryonic antigen, the most widely used tumor marker, is limited by poor sensitivity for patients with breast cancer. Most recently monoclonal antibody technology has permitted the development of CA 15-3 and CA 27.29 antigens.

CA 19-9 Tumor Marker

**Normal Findings**

<37 units/mL

**Indications**

CA 19-9 antigen is a tumor marker used for the diagnosis of patients with pancreatic or hepatobiliary cancer, evaluation of response to treatment, and surveillance.

**Test Results & Clinical Significance**

↑ Levels

- Pancreatic carcinoma - Hepatobiliary carcinoma
- Pancreatitis - Cholecystitis
- Cirrhosis - Gastric cancer
- Cholecystitis - Cirrhosis
- Gastric cancer - Colorectal cancer
- Gallstone - Lung cancer
Test explanation

CA 19-9 is a carbohydrate cell-surface antigen

Clinical Priorities

- CA 19-9 is not used as a screening test for pancreatic or hepatobiliary tumors.
- CA 19-9 is used to support the diagnosis of pancreatic or hepatobiliary tumors and to monitor patients’ response to treatment.

CA-125 Tumor Marker

Normal Findings

0-35 units/mL

Indications

CA-125 is used in the detection of ovarian cancer. It is also used to determine the extent of disease and to monitor the response to treatment.

Test Results & Clinical Significance

↑ Levels

- Malignant Disorders
- Cancer of the ovary
- Cancer of the pancreas
- Cancer of the colon
- Cancer of the lung
- Cancer of the breast
- Lymphoma

Test explanation

This tumor marker has a high degree of sensitivity and specificity for ovarian cancer. CA-125 is an extremely accurate marker for nonmucinous epithelial tumors of the ovary. It is elevated in more than 80% of women with ovarian cancer.
Prostate-Specific Antigen (PSA)

Normal Findings

<4 ng/mL

Indications

This test is used as a screening method for early detection of prostatic cancer. When the PSA test is combined with a rectal examination, nearly 90% of clinically significant cancers can be detected. This test also used to monitor the disease after treatment.

Test Results & Clinical Significance

↑ Levels
- Prostate Cancer
- BPH
- Prostatitis

Interfering Factors

Rectal examinations are well known to falsely elevate PAP levels and they may also minimally elevate the PSA. To avoid this problem, the PSA should be drawn before rectal exam of the prostate or several hours afterward. Ejaculation within 24 hours of blood testing will be associated with elevated PSA levels

Test explanation

- PSA is a glycoprotein found in high concentrations in the prostatic lumen. Levels greater than 4 ng/mL have been found in more than 80% of men with prostate cancer. The PSA assay is also a sensitive test for monitoring response to therapy.

- The PSA is limited by a lack of specificity within the ‘diagnostic gray zone’ of 4 to 10 ng/mL. PSA levels also may be minimally elevated in patients with benign prostatic hypertrophy (BPH) and prostatitis. PSA levels greater than 10 ng/mL indicate a high probability of prostate cancer. Lower values may be compatible with BPH or early prostate cancer.
Test explanation (con’t)

Prostate-Specific Antigen (PSA)

- Percent free PSA (%FPSA) is also helpful in differentiating between cancer and benign prostate disorders in men with total PSA levels within this ‘diagnostic gray zone’. It has been noted that when the %FPSA is <25%, there is a high likelihood of cancer.

- Higher free PSA with BPH

- Higher protein bound PSA with prostate cancer

Calcium, Blood (Total/Ionized Calcium, CA)

Test explanation

Serum calcium is necessary in many metabolic enzymatic pathways. It is vital for muscle contractility, cardiac function, neural transmission, and blood clotting. The most common cause of hypercalcemia is hyperparathyroidism.

Malignancy, the second most common cause of hypercalcemia, can cause elevated calcium levels in two main ways. First, tumor metastasis (myeloma, lung, breast, renal cell) to the bone can destroy the bone, causing resorption and pushing calcium into the blood. Second, the cancer (lung, breast, renal cell) can produce a PTH-like substance that drive the serum calcium up (ectopic PTH)

Beta₂ (B₂) – microglobulin

- Levels may be raised in people with multiple myeloma or other cancers of blood cells.
- This test cannot be recommended for cancer screening.
Index of Tumor Markers by Disease Site

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<td>Carcinoma</td>
<td>CA 19-9, CEA, PHI</td>
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<td>Non-beta cell tumor</td>
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<td></td>
<td>D-cell tumor</td>
<td>Gastrin (occasionally B-HCG &amp; calcitonin)</td>
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<td>CA-125</td>
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<tr>
<td></td>
<td>Endothelial carcinoma</td>
<td>CA-125 (only for advanced or recurring cases)</td>
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<tr>
<td></td>
<td>Germ cell tumor</td>
<td>AFP, B-HCG</td>
</tr>
<tr>
<td>Cervix</td>
<td>Adenocarcinoma</td>
<td>CA-125</td>
</tr>
<tr>
<td></td>
<td>Squamous cell carcinoma</td>
<td>SCCA (TA-4)</td>
</tr>
<tr>
<td>Fallopian tube</td>
<td>Carcinoma</td>
<td>CA-125</td>
</tr>
<tr>
<td>Prostate</td>
<td>Carcinoma</td>
<td>PSA, PAP, PHI</td>
</tr>
<tr>
<td>Testis</td>
<td>Non-seminomatous germ cell</td>
<td>AFP, B-HCG</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Medullary carcinoma</td>
<td>Calcitonin</td>
</tr>
<tr>
<td>Parathyroid</td>
<td>Adenoma</td>
<td>PTH</td>
</tr>
<tr>
<td>Pituitary</td>
<td>Depending on the affected secretory cell</td>
<td>Prolactin, ACTH, B-HCG</td>
</tr>
</tbody>
</table>
Hypopituitarism

Decreased function of the pituitary gland (hypopituitarism) can be caused by a dysfunction of the pituitary gland or the hypothalamus. Single or multiple hormonal deficiencies may be present. It is important to assess for other hormonal deficiencies.

- **Hypopituitary (Mass Lesions)** –
  - Pituitary adenomas are typically divided by size. Microadenomas are less than ten millimeters in diameter, and may secrete hormones or be clinically inactive. Macroadenomas are greater than ten millimeters in diameter. There is a greater incidence of microadenomas than macroadenomas. Prolactinomas are the most common type of adenoma. The most likely cause of adenoma formation is considered to be genetic mutation.
  - The clinical presentation of patients with a pituitary adenoma will depend on the hormones involved. For example; a prolactinoma can cause hypogonadism, infertility, amenorrhea and galactorrhea. A patient with a macroadenoma will typically complain of headaches and visual disturbances due to the mass effect of the tumor. (Made sure to assess visual fields upon physical examination) Macroadenomas can elevate intracranial pressure and/or cause an intracranial hemorrhage.
  - Other types of mass lesions include granulomas, brain tumors, and metastatic carcinomas.

- **Hypopituitary (Non-mass Lesions)**
  - Hypopituitarism without a mass lesion can come from several sources which include: surgery, autoimmunity, trauma, hemochromatosis, stroke, and encephalitis.

[Note: Severe illness, anorexia nervosa, malnutrition, type 2 diabetes (with obesity) and extreme prolonged exercise (in women) can cause physiologic absence or decreased function of the testes and ovaries (hypogonadotropic hypogonadism). These conditions can cause a decrease or cause a lack of FSH and LH production by the pituitary.]

(Note: Prolactinoma is the most common type of hormone secreting pituitary tumors. The cause is presently considered unknown. This type of tumor causes an increase in synthesis and secretion of prolactin causing hyperprolactinemia)
Hyperprolactinemia

Excessive secretion of prolactin cause will cause elevated serum prolactin or hyperprolactinemia. About 70% of women with secondary amenorrhea and galactorrhea (lactation in the absence of nursing) have hyperprolactinemia. Symptoms in women include: menstrual cycle disturbances, galactorrhea and infertility. Men typically present with decrease libido, erectile dysfunction, infertility and hypogonadism (decreases testosterone production).

The following is a list of the potential causes of hyperprolactinemia:

- **Physiologic**
  - Exercise
  - Pregnancy
  - Idiopathic
  - Stress
  - Nursing
  - Puerperium – the time between delivery of the baby and the six weeks after delivery

- **Pharmacologic**
  - Amoxapine
  - Amphetamines
  - Anesthetic agents
  - Antipsychotic agents
  - Cimetidine (tagamet)
  - Estrogens
  - Hydroxyzine
  - Methyldopa
  - Metoclopramide
  - Opioids
  - Nicotine
  - Phenothiazines
  - Progestins
  - Reserpine
  - Risperidone
  - Selective serotonin reuptake inhibitors
  - Tricyclic antidepressants
  - Verapamil
Pathologic
  - Cirrhosis
  - Hypothyroidism
  - Multiple sclerosis
  - Hypothalamic disease
  - Prolactin-secreting tumors
  - Renal failure
  - Spinal cord lesions
  - Systemic lupus erythematosus

Summary

It’s important to remember that the hypothalamus and the pituitary gland are at the beginning of the “top down” approach to addressing endocrine imbalances. Also keep in mind the neurological connection, and influence of the limbic system on endocrine function. Due to the wide range of signs and symptoms due to hypothalamic and pituitary dysfunction, the practitioner must assess for disorders originating from the hypothalamus and pituitary when evaluating for any endocrine dysfunction. Once again a comprehensive history, physical examination and basic functional medicine lab tests are the foundations to achieve an accurate diagnosis.

Required reading: “Increased 5-Lipoxygenase Immunoreactivity in the Hippocampus of Patients with Alzheimer’s Disease” This article can be found in the download library on www.FunctionalMedicineUniversity.com

References

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3. 2009 Current Medical Diagnosis and Treatment, 48th edition, Stephen J. McPhee, MD, Maxine A. Papadakis, MD