

Hormone Circuits Lecture notes

Uri Alon (Spring 2021)

Lecture 9

The thyroid and its discontents

Goal: Understand the biology and diseases of thyroid, to set up the next lecture on the origin of autoimmune diseases

The HP axes control pillars of life- growth, reproduction, stress, and metabolism. So far, we studied two, the HPA axis for stress, and the HP-Ovary axis for ovulation. We now study a third, the HP-thyroid axis, or HPT axis for short, that controls metabolic rate. It is biologically fascinating, and the origin of many common diseases. Especially diseases in which the body attacks itself- autoimmune diseases. So, this lecture is the first of a two-lecture mini-series, where we understand the origin of autoimmune diseases: what is the logic of the body attacking itself. Today we will use the thyroid to understand the biology, dynamics, and treatment of such diseases. To do so, we will revisit some of the principles that we studied, to reap the fruit of our work in this course by understanding otherwise mysterious features of these diseases.

The HPT axis is designed to keep a steady level of thyroid hormone T4

The thyroid is a 10-gram gland at the front of our throat shaped like a butterfly (Fig. 1). It secretes thyroid hormone, T4, that goes to all cells and has far-reaching effects on the heart and on metabolism. It is the effector organ of the HPT axis (Fig. 2). The hypothalamus H secretes hormone x1 (thyroid releasing hormone TRH), that makes the pituitary P secrete hormone x2 (thyroid stimulating hormone) from specialized thyrotroph cells. TSH makes the thyroid secrete T4, our x3 hormone. T4 is converted in the tissues to a more active form T3. As in all HP axes, T4 inhibits the production of the two upstream hormones x2 and x1, TSH and TRH.

As in the other HP axes, the hormones also control the size of the glands. TSH makes the thyroid cells proliferate and grow. In fact, growth of the thyroid is infamous, it is called goiter. It happens when iodine, essential for making T4, is low in the diet, as in areas far from the sea which in old times lacked access to the iodine in seafood. Low T4 releases the inhibitors from TSH, and makes the thyroid grow sometimes by a factor of 10, like a small melon at the throat, to try to make enough thyroid hormone.

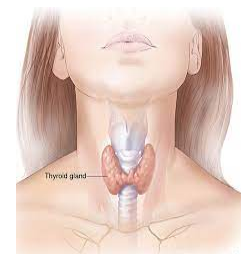


Figure 1

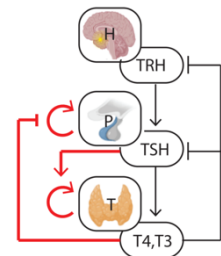


Figure 2

You can already see that when T4 is low, TSH is high (Fig. 3). TSH is a very sensitive indicator of problems with the thyroid. It varies by a factor of a thousand while T4 varies by a factor of less than 10, with a normal range of 10-20 pmol/L. The relation between TSH and T4 is steep, almost exponential. That is why TSH is such a common blood test. It can even tell if there will be future problems, even though now T4 is fine- stay tuned.

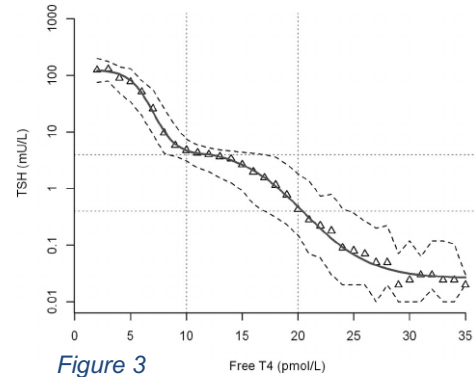


Figure 3

The pituitary cells that secrete TSH also have size control- in this axis, it is T4 that inhibits P cell growth. This is a variation on the other axes (where x_1 enhances P growth, not x_3 inhibits it). Why this different design? Perhaps this axis is designed to keep constant T4 levels, whereas other axes like the HPA are designed to have a wide range of x_3 (cortisol) according to the stress inputs. Indeed, the equation for P in the HPT axis reads $dP/dt = P(b_P/x_3 - a_P)$. This locks x_3 to a constant steady-state $x_3 = b_P/a_P$ equal to the ratio of P cell production and removal parameters. In contrast, in the HPA axis, $dP/dt = P(b_P x_2 - a_P)$ which locks x_2 to a constant $x_2 = a_P/b_P$, and keeps x_3 free to vary with input u .

Indeed, free T4 levels in the circulation are rather constant. We say free T4 because most of T4 is bound in the blood to carrier proteins and is not active. The normal free T4 range in the population is 10-20 pmol/L as mentioned above, and a given healthy individual varies around their own personal set point over about 50% of this range.

In some situations, the setpoint can change, however. The hypothalamus sends signals to change the setpoint. One such case is starvation or serious illness, in which both TSH and T4 are held low to reduce metabolic activity. This is called sick euthyroid syndrome. Another signal that can change T4 is temperature, where cold climate increases T4 because it has a role in thermogenesis (making heat).

The crazy production pipeline of T4

For our understanding of diseases, we need some details of how t4 is made in the thyroid. T4 is a molecule made of two carbon hexagonal rings from tyrosine (Fig. 4). Each ring has two iodines attached. In the cells of the body, T4 is converted to a more active form T3, so called because one of four iodines is removed by iodinase enzymes, leaving three iodines.

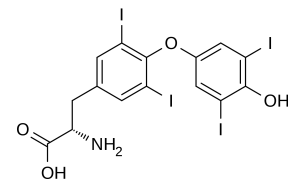


Figure 4

T4 is made in modular 'chemical factories' in the thyroid called the thyroid follicles (Fig. 5). Each follicle is a layer of epithelial cells called thyrocytes surrounding a spherical pore filled with colloid. Total size is about 400 microns. The thyrocytes import iodine from the blood vessels surrounding the follicle, then export the iodine into the colloid (Fig. 6). They make huge amounts of a protein Tg that has many tyrosines, and dump this also into the colloid. There, iodine is added to the tyrosines by an enzyme on the surface of the thyrocytes called TPO. TPO also links two tyrosines together to make T4. Then, the cells import the iodinated Tg back inside, break it up into small pieces, and extract the T4, and export it out of the cell into the circulation. Crazy, no?

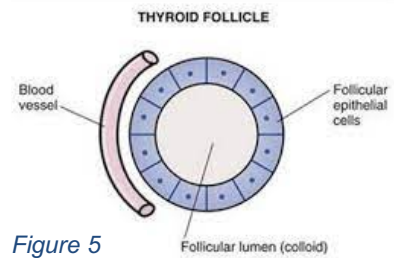


Figure 5

Remember Tg and TPO for future use. TSH increases all of the above steps, and the production of Tg, TPO and the other pumps and enzymes.

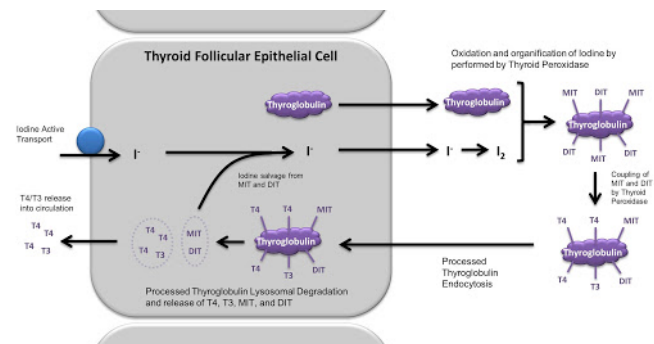


Figure 6

Hyperthyroidism and hypothyroidism

To understand the importance and function of T4, let's see what happens when there is too much or too little of it. Diseases with too much T4 result in **hyperthyroidism**. The heart beats fast and irregularly, which can lead to dangerous arrhythmias. You eat more but lose weight. This harks back to our first lecture, where we saw the appetite and diet lines. Hyperthyroidism increases metabolic rate and shifts the diet line towards the opposite effect of higher food intake and reduced fat. Emotions and thoughts race, sometimes resembling mania. There is a feeling of heat and sweat, due to thermogenesis. Muscles hurt. Hands might shake due to effects on the nervous system.

When thyroid hormone is too low, **hypothyroidism**, the effects are opposite. The heart beats slowly and weakly, and you can be out of breath when climbing the stairs. You gain weight despite not eating more, with reduced appetite and constipation. Emotions tend towards depression. There is a clammy feeling of cold. In infants, hypothyroidism can lead to cognitive problems due to impaired development of the brain- that is why a TSH test at birth is so critical.

Hashimotos disease, a case of self-attack

The most common cause of hypothyroidism is Hashimoto's disease (Fig. 7). Devastatingly common, it affects 4% of the population, primarily women. In Hashimoto's disease, white blood cells called T-cells attack and kill thyrocytes. Antibodies against thyrocytes participate in the damage.

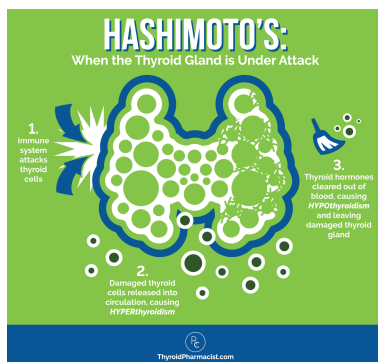


Figure 7

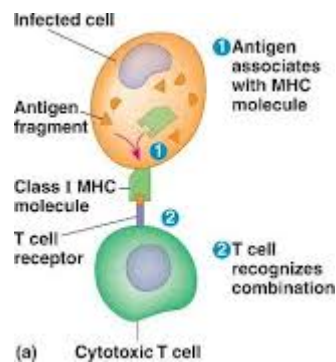


Figure 8

The T-cells normally attack virus infected cells, not healthy cells of the body (Fig. 8). Cells in the body display small pieces of the protein they make on “identity cards” on their surface called MHCs. When a virus infects a cell, it displays pieces of the virus proteins in some of its MHCs. The MHCs are scanned by T cells. Each T-cell has a special receptor called the TCR, which can sense specific pieces of protein, called **antigens**, in an MHC. If a T-cell recognizes the viral antigen, it kills the cell by injecting poison and setting off suicide pathways. T-cells that sense normal body proteins are eliminated in an “education” process, and so the only remaining T cells respond to foreign proteins and can eliminate virus infected cells. The T-cells also activate B-cells to make **antibodies** against the same targets, and the antibodies mark the virus for destruction.

Unfortunately, in Hashimotos, T-cells attack healthy thyrocytes and damage the thyroid. More in the next lecture.

The antigens recognized by T -cells in Hashimotos are pieces of the Tg and TPO enzymes discussed above.

The T-cells also activate B-cells to make antibodies against Tg and TPO. The antibodies participate in damaging the thyroid. Hashimotos is clinically identified by anti-Tg and Anti-TPO antibodies in the blood.

Sometimes, early stages of Hashimoto's cause T4 to spill from destroyed cells, causing hyperthyroidism. This is soon followed by hypothyroidism as the thyroid is destroyed.

Hashimotos is treated by supplying T4 in pills. The pills are taken for life since the autoimmune attack never stops (though it can come in waves). Most people live fine with these pills. A small percentage has problems adjusting the dose. Thus, this causes problems for millions of people.

TSH shows a delay after Hashimoto's is treated

When Hashimoto's is treated by T4 pills, T4 recovers to its normal range comparatively rapidly. TSH however remains high for 6 weeks after T4 normalizes (Fig. 9). This delay is usually not explained in endocrinology textbooks. It cannot be explained by the protein lifetimes which are much faster.

In fact, the disease can start quietly with no symptoms, long before T4 levels drop below normal (Fig. 10). In this **subclinical** stage, thyroid cells are killed by the immune system. TSH is high (above 5IU), but T4 is normal. The origin of the subclinical stage is the dynamical compensation we discussed before. The pituitary cell total mass grows and so more TSH is secreted, to compensate for the killing of thyrocytes.

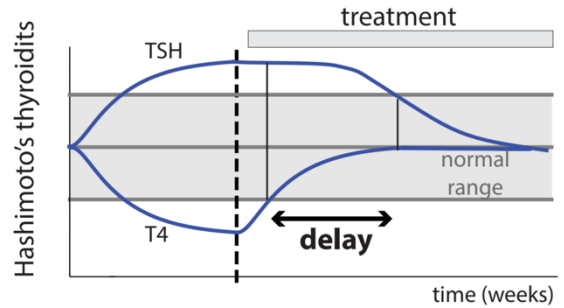


Figure 9

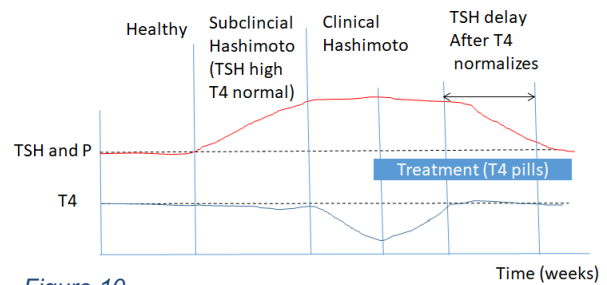


Figure 10

To understand the subclinical stage in terms of equations, we can build on our experience with the HPA axis. The thyroid mass growth is stimulated by TSH, denoted x_2 , so that $dT/dt = T(b_T x_2 - a_T)$. The steady state of TS, $x_2 = a_T/b_T$, is proportional to the removal rate of thyroid cells, a_T . The autoimmune killing increases thyrocyte removal rate a_T , so that Hashimoto raises TSH, as observed. The pituitary mass grows to supply this extra TSH. However, the level of T3, denoted x_3 , is kept constant by the previously mentioned equation for the pituitary mass

$dP/dt = P(b_p / x_3 - a_p)$, so that $T4 = x_3 = a_p/b_p$. Clinically, doctors recommend a followup to see if T4 levels fall below their normal range.

Eventually however, the pituitary cannot grow beyond its carrying capacity. We need a more accurate equation with carrying capacity K : $dP/dt = P(b_p(1 - P/K) / x_3 - a_p)$. Now x_3 drops and we have overt hypothyroidism, the clinical stage of the disease. These dynamical findings are by Yael Korem, who just finished her PhD in our group.

Hyperthyroidism due to toxic nodule: a case of a hypersensing mutant

We now turn to hyperthyroidism, too much T4. One major cause is a batch of growing cells in the thyroid that form a nodule that secretes too much T4 (Fig. 11). These can be imaged by ultrasound, felt by touch, and seen to be active in secreting T4 by a radioactive iodine scan. Since they show up on the scan, they are called 'hot nodules' or **toxic nodules**. They occur in about 1% of the population.

There are also so called 'cold nodules' that do not secrete T4. Cold nodules are 10 times more likely than hot nodules to become cancerous (to have the potential for cancer in other body parts called metastases). Hot nodules are very rarely cancerous.

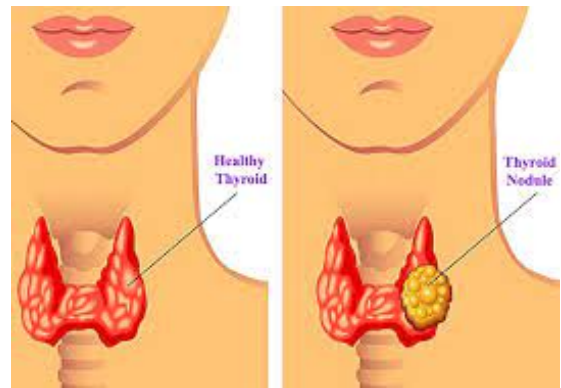


Figure 11

Toxic nodules are an example of a principle we have seen before. The thyroid cells are controlled by a feedback circuit in which a signal, TSH, makes the cells both secrete more hormone and to proliferate. We have seen this in the beta cell circuit where glucose is the signal. This circuit has a fragility. Mis-sensing mutants that "think" there is too much signal can divide and form a nodule that secretes too much hormone.

This is exactly what happens in a toxic thyroid nodule. The nodule cells are all copies (a clone) of a mutant cell with a mutation, usually in the TSH receptor, that makes it more sensitive to TSH. There are at least 50 such known mutations in the receptor gene. The mutant proliferates and over many years can grow to a toxic nodule that causes hyperthyroidism.

Treatment of toxic nodules is their removal.

It is interesting to consider why the thyroid does not have a biphasic mutant resistance mechanism like beta cells, where cells that sense too much glucose kill themselves (Fig. 12). This effect, called glucotoxicity, gives strong missensing mutants a selective disadvantage. We discussed this in lecture 3-4.

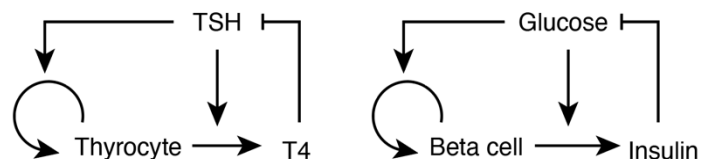


Figure 12

Why does the thyroid lack a biphasic effect, something we might call TSH-toxicity? It would be nice if a cell that senses high TSH would kill itself to avoid toxic nodules. However, unlike beta cells, the signal in the thyroid case, TSH, varies over a 1000-fold range to compensate for physiological variation, such as iodine levels in the nutrition which can vary over at least a 100-fold range. Blood glucose has a much smaller range of variation. Perhaps the thyroid is thus prevented from using a TSH-toxicity due to its need for extensive compensation. In the next

lecture we will see how the need for mutant resistance can explain the physiological role of autoimmune attack of the thyroid. But we are getting ahead of ourselves.

Graves disease, a common autoimmune disease shrouded in mystery

An even more common cause of hyperthyroidism, too much thyroid hormone, is Graves disease. It occurs often at ages 20-50, in as much as 2-3% of the population, more in females than males.

In Graves disease, the body produces antibodies that bind and activate the TSH receptor. They thus mimic TSH. As a result, the thyroid grows and secretes more T4. As in Hashimoto's, there is a subclinical stage with low TSH and normal T4. The pituitary shrinks, or more accurately the total mass of TSH-secreting cells in the pituitary shrinks. TSH drops to undetectable levels. When the pituitary shrinks to very small mass, T4 begins to rise, and the clinical stage sets in.

Graves is treated differently in the US and in Europe/Israel. In the US the thyroid is typically destroyed by radioactive iodine or removed, and the person takes T4 pills for life. In Europe, often the thyroid is first given a chance. The patient takes antithyroid drugs that inhibit T4 production by inhibiting TPO. T4 levels normalize. Remarkably, in about 50% of the patients, Graves goes away: antithyroid drugs are reduced (tapered) over months until after a year or so T4 and TSH return to normal and one can stop taking drugs, the antibodies go away. In the rest of the 50% of the patients, Graves doesn't go away, and the thyroid is removed. Most patients also take beta-blocker drugs to alleviate the heart palpitations and muscle tremors that characterize Graves' disease.

Note that here again there is a delay, and it is even longer than in Hashimoto's (Fig. 13). After T4 normalizes it takes months for TSH to go back up to normal. Again, this delay is due to pituitary mass. During Graves the pituitary thyrotrophs atrophy and take months to recover.

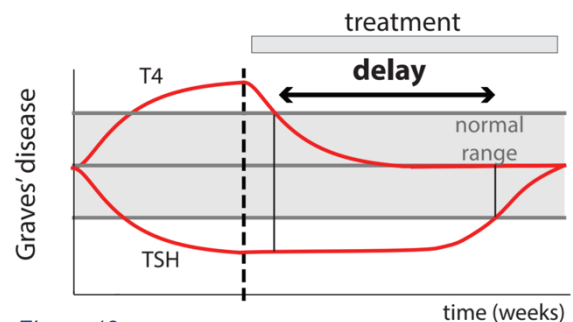


Figure 13

Why are there autoimmune diseases of hormone glands?

Why is the thyroid attacked by the body? Why risk 5% of the population with a potentially deadly disease, before medicine turned it into a curable disease? The same question for beta cells, where type-1 diabetes is an autoimmune attack on beta cells that was a death sentence to about 1% of children before the advent of insulin treatment.

Also, why these particular cell types and not others? For example, right next to the beta cells are alpha cells that produce glucagon. Why is there no autoimmune disease that attacks alpha cells? Similarly, there is almost no autoimmune disease of the parathyroid gland, which sits right on top of the thyroid. The parathyroid cells, which make parathyroid hormone for calcium control, are almost never attacked. They are only attacked after immune checkpoint drugs are taken for cancer treatment, or in very rare congenital mutations in immune tolerance.

And why the weird antibodies that activate TSH receptors in Graves disease? Where are the corresponding antibody diseases for the thousands of other types of receptors in the body?

If you want to consider some answers, and you have a curious mind, tune in to the next lecture in our 2-lecture miniseries.

I am just a T cell and my stories seldom told

Educated in the thymus

I learned how to defend my country

Laying low

seeking out the lonely lymph nodes where the other T cells go

Seeking out the places only they would know

Nay nay nay...

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