

## How Do We Know the Hypothalamus Controls the Anterior Pituitary Gland?

*What is the hypothalamus and anterior pituitary gland? What are releasing hormones?*

The hypothalamus is a small area of the brain located just below the thalamus. Despite its small size, it serves many very important functions for survival. The hypothalamus is involved in the regulation of body temperature, hunger, thirst, circadian rhythm, etc. The hypothalamus is also known to synthesize and secrete neurohormones to control the anterior and posterior pituitary gland. However, the main focus of this text is to describe the neurohormonal control of the anterior pituitary gland. The neurohormones secreted by the hypothalamus are referred to as *releasing hormones*.

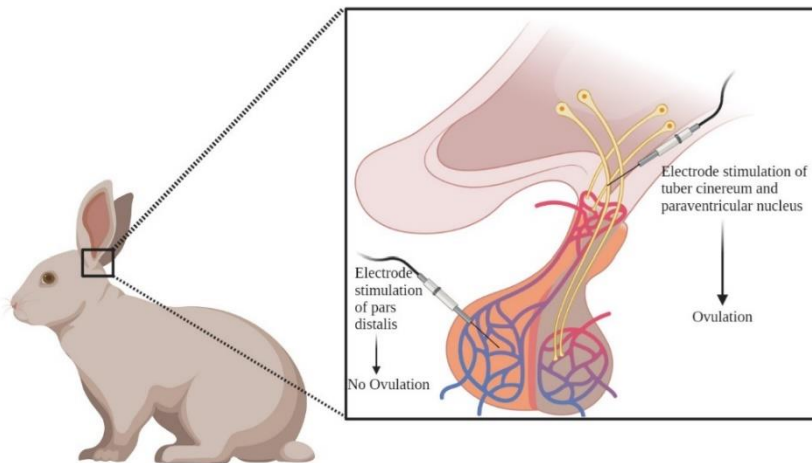
Releasing hormones are tropic hormones. In other words, releasing hormones control the release of other hormones. How do releasing hormones control other hormones? How does the hypothalamus directly and indirectly control other endocrine glands? As previously mentioned, the hypothalamus directly controls the anterior pituitary gland via the secretion of releasing hormones. The hypothalamus

contains a portal system of capillaries called the hypothalamo-hypophyseal portal vessels (HHPV) that aid its communication with the anterior pituitary gland. When the hypothalamus receives stimulation from another region of the brain, it will synthesize a hormone according to the message it received. The hormone will then be sent down to the median eminence via hypothalamic nuclei. The median eminence the part of the HHPV that creates a link between the hypothalamus and anterior pituitary. After the hormones enter the HHPV, they are secreted into the anterior pituitary gland and bind to their designated receptors. Upon binding, they stimulate the production and secretion of another hormone which will be sent out to peripheral endocrine organs via the bloodstream.

*How do we know the hypothalamus controls the anterior pituitary? What hypotheses and experiments were performed?*

During the early to mid-1900s, there was a lot of debate surrounding how the anterior pituitary and hypothalamus worked together. In fact, in the 1930s Gregory Popa and Una Fielding, who were the first to describe the HHPV as a portal system, hypothesized that the blood flow went in the direction of the hypothalamus. This hypothesis was formed due to earlier studies suggesting that there were internal secretions that moved from the posterior pituitary gland to the hypothalamus. Therefore, they assumed the direction of informational flow would be the same in the anterior pituitary.

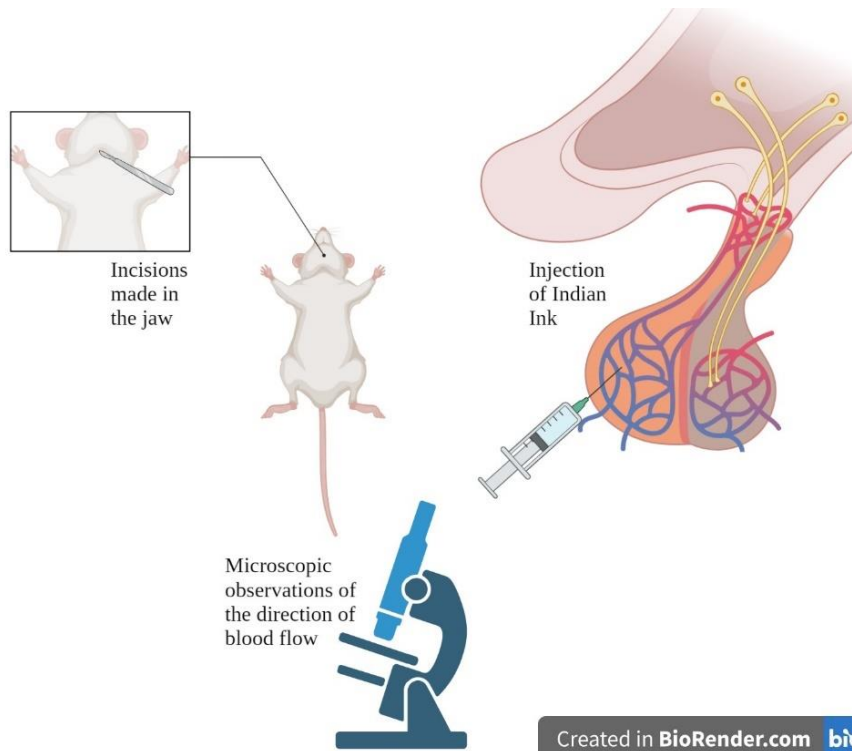
However, the researcher Geoffrey Harris would soon spend his life's work going against this theory after inspiration from the work of Francis Marshall. In the 1930s, Marshall suggested that there is a reflex pathway triggered by sensory stimuli that affect secretions from the anterior pituitary gland during reproductive cycles. By the 1940s it was generally accepted that this was the case, but it was still unclear what part of the brain and how the brain controlled the anterior pituitary. Therefore, Harris



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**Figure 1 Harris induces ovulation through electrical stimulation.** One of many experiments performed by Geoffrey Harris was the method he developed for the electrical stimulation of the hypothalamus and anterior pituitary. In his study he found that stimulating the hypothalamus induced ovulation, but stimulation to the anterior pituitary did not induce ovulation. This supported the possibility that the hypothalamus controls the anterior pituitary because it was well known at the time that the anterior pituitary was involved with ovulation and reproductive cycles in mammals.

made the hypothesis that it was instead the hypothalamus controlling the anterior pituitary and not the other way around. In 1930s and 1940s, Harris used electrical stimulation to the hypothalamus and anterior pituitary in rabbits to see if they would continue to ovulate (**Figure 1**). In the study he used rabbit holders to stabilize and immobilize the rabbit head for the procedure. Connected to each rabbit holder was a circuit and primary coil electrodes



**Figure 2 Harris and Green observe the direction of flow in the HHPV.** A visual depiction of the anatomical study performed by Geoffrey Harris and John Green in the 1940s. An incision was made in the rat upper jaw to access the hypothalamus and anterior pituitary. Indian Ink was injected into the portal vessels for greater visibility under the microscope. Direction of flow was found to go from the hypothalamus to the anterior pituitary.

which he sent electrical pulses through to stimulate different regions of the hypothalamus and anterior pituitary. Only two stimulated regions produced an ovulatory response. Those two regions were the tuber cinereum and the paraventricular nucleus. The tuber cinereum is the part of the hypothalamus that connects to the median eminence and anterior pituitary. The paraventricular nucleus is also part of the hypothalamus and has neurons connecting to the posterior pituitary but also secretes releasing hormones to the anterior pituitary. However, these facts were not known at this time.

In the anterior pituitary he stimulated the pars distalis. The pars distalis is the main portion of the anterior pituitary that synthesizes hormones that are regulated by releasing hormones from the hypothalamus. However, at this time it was not known that the hypothalamus controlled their release. Curiously, stimulation to the pars distalis in the anterior pituitary gave no ovulatory response, even after an extended period of stimulation. This further insinuated that the hypothalamus is likely a key regulator of the anterior pituitary. However, Harris still believed that more anatomical data was needed to fully understand the mechanism of control.

### *Anatomical Observations*

In 1949, Harris and his colleague, John Green, performed the first observational study in living mammals. Their results indicated that blood in the HHPV flowed from hypothalamus to anterior pituitary (**Figure 2**). In the study they used rats because they have a long HHPV which makes them easier to observe. They opened the mouths of the rats and made surgical incisions to the soft palate of the upper jaw to remove it so they could gain access to the skull. When they removed the small portion of the skull covering the hypothalamus, they injected Indian Ink into the HHPV. This made it easier to see the blood flow under the microscope. In all 12 rats that they used they clearly saw the blood flowing from the median eminence down to the pars distalis.

### *Concluding Remarks*

Unfortunately, the experiments described in the text are extremely few in comparison to the true timeline of experiments and researchers. However, the complete works from Harris on the hypothalamus and anterior pituitary contributed heavily to a shift in what was believed among neuroendocrinologists at the time. Following Harris's experiments, many researchers, including Harris himself, sought to confirm his original results that the anterior pituitary is in fact controlled by the hypothalamus.