

REVIEW ARTICLE

Parallel trajectories in the discovery of the SCN-OVLT and pituitary portal pathways: Legacies of Geoffrey Harris

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Abstract

A map of central nervous system organization based on vascular networks provides a layer of organization distinct from familiar neural networks or connectomes. As a well-established example, the capillary networks of the pituitary portal system enable a route for small amounts of neurochemical signals to reach local targets by traveling along specialized pathways, thereby avoiding dilution in the systemic circulation. The first evidence of such a pathway in the brain came from anatomical studies identifying a portal pathway linking the hypothalamus and the pituitary gland. Almost a century later, we demonstrated a vascular portal pathway that joined the capillary beds of the suprachiasmatic nucleus and a circumventricular organ, the organum vasculosum of the lamina terminalis, in a mouse brain. For each of these portal pathways, the anatomical findings opened many new lines of inquiry, including the determination of the direction of flow of information, the identity of the signal that flowed along this pathway, and the function of the signals that linked the two regions. Here, we review landmark steps to these discoveries and highlight the experiments that reveal the significance of portal pathways and more generally, the implications of morphologically distinct nuclei sharing capillary beds.

KEYWORDS

angiome, blood flow, circumventricular organ, hypothalamus, iDisco, neurohormones

1 | INTRODUCTION

1.1 | Portal pathways in the brain and the importance of vascular communication

A map of central nervous system organization based on vascular networks or angiomes¹ provides a layer of organization distinct from familiar neural networks or connectomes. As a well-established example, the capillary networks of the pituitary portal system enable a route for small amounts of neurochemical signals to reach local targets by traveling along specialized pathways, thereby avoiding dilution in the systemic circulation. Anatomical studies provided the first evidence of this vascular pathway in the brain. Specifically, Popa and Fielding^{2,3} identified a portal pathway linking the hypothalamus and the pituitary gland. Their anatomical work was based on hematoxylin

and eosin-stained sections of the human brain. They also extensively discussed previous studies of this brain region. Based on the available literature and the appearance of India ink in the hypothalamus after it had been injected into the anterior pituitary, they vigorously argued that the direction of blood flow was from the pituitary gland to the hypothalamus.

“... in 1930, we stated the fact that there is a system of veins taking origin from the sinusoids of the buccal portion of the hypophysis and from the capillaries of the neural portion, which ascend through the stalk to the region of the floor of the infundibular recess of the 3rd ventricle where they break up into a secondary capillary net. As they ascend, these run first in the substance of the pars tuberalis, mostly in front of the stalk,

and then at various levels penetrate into the neural portion of the stalk and ascend within 'glial sleeves' towards the floor of the infundibular recess, where they lose their glial wrapping and break up into the secondary net"²

Almost a century later, we demonstrated a vascular portal pathway joining the capillary beds of the suprachiasmatic nucleus (SCN) and a circumventricular organ, the organum vasculosum of the lamina terminalis (OVLT), in a mouse brain.⁴ For each of these portal pathways, the anatomical findings opened many new questions and lines of inquiry, including the determination of the direction of the flow of information, the identity of the signal that flowed along this pathway, and the function of the signals that linked the two regions.

Although the portal pathway had been identified anatomically, definitive proof of its importance required much more research. It was important to identify the putative chemical(s) that flowed within this pathway, to determine the source and target of the chemical(s), to characterize the chemical(s) itself, and to determine its function. In the case of the pituitary portal system, it took decades after the anatomical characterization of portal vessels to find definitive proof regarding its importance. Today, an opus widely credited with resolving the question of the direction of communication between hypothalamus and pituitary is Harris's 1955 book (*Neural Control of the Pituitary Gland*⁵). Despite the positive review of his book, it took many years of intense competitive research activity, a huge amount of money, large numbers of animals, and the Nobel prize-winning work (1972) of Guillemin and Schally,^{6,7} to definitively identify the neurosecretions that flow in the pituitary portal system. A timeline of landmarks and discoveries lays out the work that must be performed for the SCN-OVLT neurovascular pathway.

1.2 | Goal of the present review

We aim to document the enormous numbers of Harris's experimental studies (with collaborators) that contributed to his thinking about hypothalamic–pituitary relationships. A second goal is to identify landmark events in the establishment of the pituitary portal system as a signaling pathway between the hypothalamus and the pituitary and to describe parallels in the landmark studies of the SCN-OVLT portal pathways. Discoveries in each of these portal pathways involve the following elements: delineation of the anatomy proving the existence of a vascular connection between the capillary beds of anatomically distinct regions, demonstrating the existence of such a portal pathway in several species, tissue transplant studies proving the existence of a diffusible neurochemical signal, determination of the direction of blood flow to determine the source and target of chemical neurosecretions, and identification of the chemical secretions that travel in the portal vasculature. We describe the decades-long time interval and sometimes hostile debate from the work of Popa and Fielding to the definitive determination of the direction of blood flow in the case of the pituitary portal system and indicate how currently available

methods hasten discovery. Finally, we consider the possibility of additional portal pathways between circumventricular organs and adjacent neuropil.

1.3 | Why do we care?

Highlighting the immense importance of these two portal systems is the fact that, although each system involves signals from a relatively small population of neurons to a local target, the downstream consequences are global, impacting tissues and organs throughout the entire body (Figure 1). In the case of the pituitary gland, hormonal secretions reach their targets via the systemic blood supply. In the case of the SCN-OVLT, we consider that the flow of information is most likely from the clock to the OVLT. In that case, the signal from the SCN reaches a target in the OVLT, which in turn communicates throughout the brain via the cerebrospinal fluid. There is a vast literature from our lab and many others on the body-wide effects of each of these systems.^{8–11}

2 | LANDMARKS IN THE ESTABLISHMENT OF THE PITUITARY PORTAL SYSTEM: 1930–1972

Harris's book, *Neural Control of the Pituitary Gland*,⁵ is often credited with being the document that led to the acceptance of the notion of a portal system in which the brain regulated pituitary hormones. However, Harris studied this problem for decades prior to publishing his book (Figure 2, Table 1). His work was based on functional, anatomical, transplant, and vascular studies, as well as a substantial number of careful literature reviews. Impressively, very early on, Harris postulated that transmission of information occurred from the median eminence to the anterior pituitary while recognizing that definitive information was lacking.¹² He spent his research life gathering definitive studies.

It is widely accepted that, before Harris's work, it was not known how the brain communicated with the endocrine system.^{13–21} It was well appreciated, however, that external stimuli, such as environmental cues related to seasons and availability of food and water, influenced hormones and behavior. The underlying mechanisms, however, were unknown, and research areas now known as "Neuroendocrinology" or "Behavioral Endocrinology" were non-existent.^{3,22,23} Harris's lifelong work focused on how the hypothalamus communicated with the endocrine system. For decades, he performed a great number of studies and wrote many review papers on the topic. The depth and quality of Harris's contributions is evident in a timeline of his publications up to the time of the publication of his book in 1955 (Table 1).

2.1 | Anatomical studies of the pituitary vascular portal system

The earliest evidence of the existence of a portal vascular pathway from the brain to the pituitary came from anatomical studies. In their

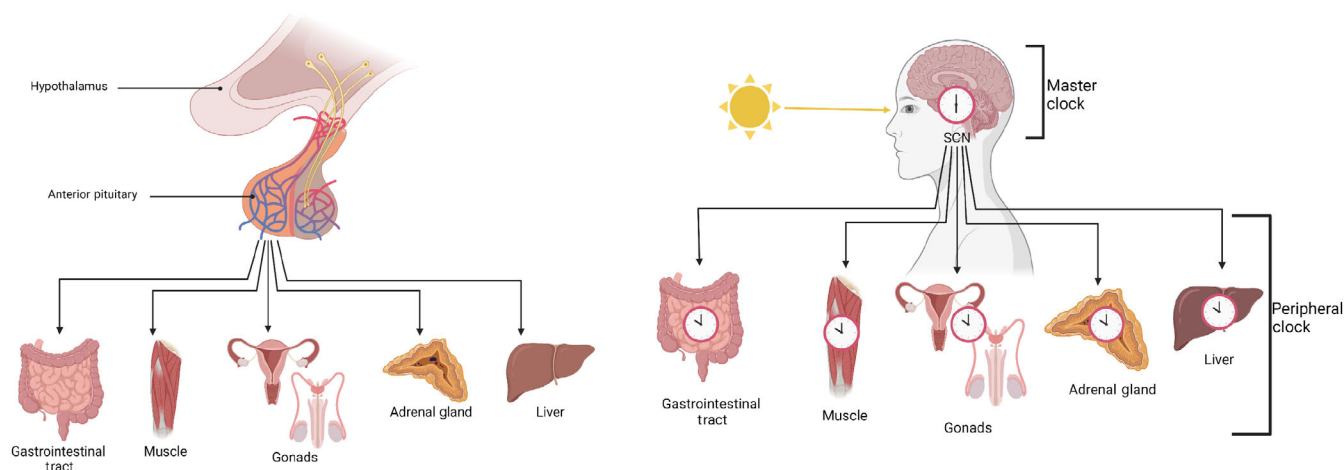
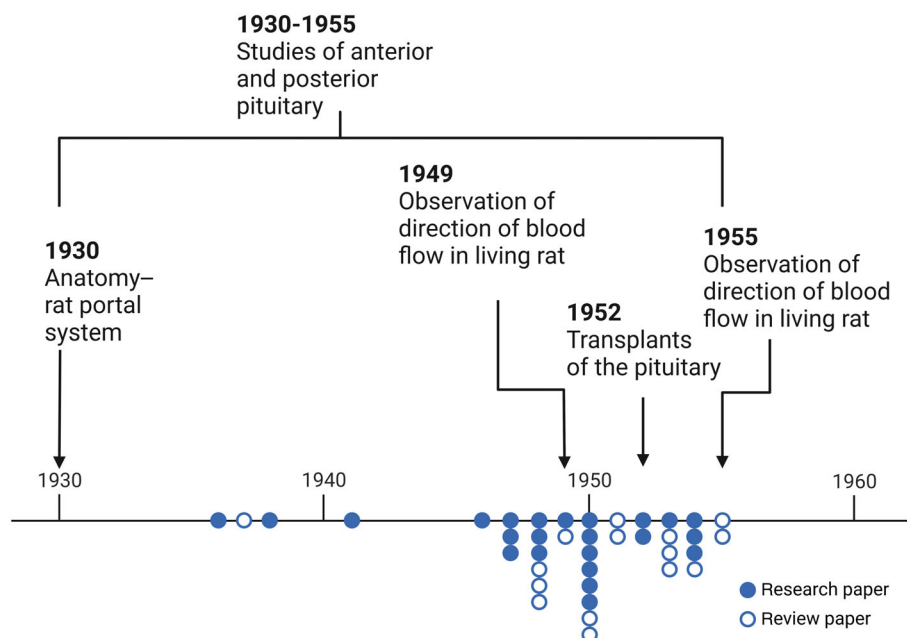


FIGURE 1 A small population of hypothalamic neurons achieves a broad, body-wide impact. Left: The neurosecretory neurons of the hypothalamus produce releasing hormones such as corticotropin-releasing factor, gonadotropin-releasing hormone, and so forth. These peptides travel to the median eminence and reach the anterior pituitary gland via the pituitary portal system. Pituitary hormones act on tissues throughout the body. Right: The suprachiasmatic nucleus (SCN) acts as a brain clock. Retinal input to the SCN enables the brain clock to synchronize with local time, and output from this clock sets the phase of oscillators in organs and tissues throughout the body.

FIGURE 2 Harris's timeline of publications up to 1955. The timeline highlights Harris's steady stream of empirical papers (open circles) and thoughtful reviews (closed circles) in the years leading to the publication of his famous, field-defining book in 1955.



preliminary note,³ Popa and Fielding provided no data but stated their claim as follows: “We have observed in the stalk(s) of the human pituitary a system of vessels arranged after the manner of a portal system, which we propose to call the hypophyseal-portal veins”. In their subsequent paper,² they provided photomicrographs of hematoxylin and eosin-stained serial sections documenting their work. Popa and Fielding's anatomical findings were quickly confirmed and accepted. This was partly because the neurovascular portal pathways are so highly conserved in vertebrate brains. Harris and his collaborators were among those who contributed anatomical evidence for a neurovascular link between the hypophysis and anterior pituitary gland. They showed, in rats, rabbits, blue whales, monkeys,

and humans, that the vascular link of the anterior pituitary was distinct from the neural innervation of the posterior pituitary.²⁴⁻²⁷

2.2 | Functions of the hypothalamus-pituitary communications

Harris's earliest publications focused on mechanisms whereby the brain-controlled ovulation in the rabbit and pseudopregnancy in the rat. The rabbit, an induced ovulatory, produces a surge of gonadotropin-releasing hormone following stimulation of the perivaginal region, such as occurs during mating. In rats, pseudopregnancy is

TABLE 1 G.W. Harris Publications.

Year	Reference
1936	Harris GW (1936). The induction of pseudo-pregnancy in the rat by electrical stimulation through the head. <i>J Physiol</i> , 88(3), 361–367. https://doi.org/10.1113/jphysiol.1936.sp003446 . ²⁸
1937	Harris GW (1937). The Induction of Ovulation in the Rabbit, by Electrical Stimulation of the Hypothalamo-hypophysial Mechanism. <i>Proc Royal Soc B</i> , 122(828), 374–394. https://doi.org/10.1098/rspb.1937.0031 . ¹²
1938	Harris GW (1938). A Technique for Operations on the Hypothalamo-Hypophysial Region of the Rabbit. <i>J Anat</i> , 72(Pt 2), 226–233. PMID: 17104686. ³¹
1941	Harris GW (1941). Further evidence concerning the role of the hypothalamus in the induction of ovulation in the rabbit following injections of copper acetate. <i>J Physiol</i> , 100(2), 231–232. https://doi.org/10.1113/jphysiol.1941.sp003936
1946	Green JD, & Harris, G. W. (1946). The neurovascular link between the neurohypophysis and adenohypophysis, <i>J Endocrinol</i> , 5(5), 136-NP. https://doi.org/10.1677/joe.0.0050136
1947	Harris GW (1947). The blood vessels of the rabbit's pituitary gland, and the significance of the pars and zona tuberalis. <i>J Anat</i> , 81(Pt 4), 343–351. PMID: 17105039. ²⁴
1947	Green JD, & Harris, G. W. (1947). The neurovascular link between the neurohypophysis and adenohypophysis. <i>The J Endocrinol</i> , 5(3), 136–146. https://doi.org/10.1677/joe.0.0050136 . ²⁷
1947	Harris GW (1947). The innervation and actions of the neuro-hypophysis; an investigation using the method of remote-control stimulation. <i>Philos Trans R Soc B: Biol Sci</i> , 232(590), 385–441. https://doi.org/10.1098/rstb.1947.0002
1948	Harris GW (1948). Electrical stimulation of the hypothalamus and the mechanism of neural control of the adenohypophysis. <i>J Physiol</i> , 107(4), 418–429. https://doi.org/10.1113/jphysiol.1948.sp004286 . ³²
1948	Harris GW (1948). Hypothalamus and pituitary gland with special reference to the posterior pituitary and labour. <i>Br Med J</i> , 1(4546), 339–342. https://doi.org/10.1136/bmj.1.4546.339
1948	Harris GW (1948). Neural control of the pituitary gland. <i>Physiol Rev</i> , 28(2), 139–179. https://doi.org/10.1152/physrev.1948.28.2.139
1948	Harris GW (1948). Regeneration of the hypophysial portal vessels. <i>Nature</i> , 162(4133), 70. https://doi.org/10.1038/163070a0 . ⁴¹
1948	Harris GW (1948). Stimulation of the supraoptico-hypophysial tract in the conscious rabbit with currents of different wave form. <i>J Physiol</i> , 107(4), 412–417. https://doi.org/10.1113/jphysiol.1948.sp004285
1948	Harris GW (1948). The hypothalamus and water metabolism. <i>Proc R Soc Med</i> , 41(10), 661–666. PMID: 18100746. ⁴⁰
1949	Green JD, & Harris, G. W. (1949). Observation of the hypophysio-portal vessels of the living rat. <i>J Physiol</i> , 108(3), 359–361. PMID: 18149770. ⁵⁰
1949	Harris GW (1949). Ovulation in the rabbit. <i>J Anat</i> , 83(Pt 1), 82. PMID: 18224834
1949	Harris GW (1949). Pituitary stalk in relation to oestrous rhythm and pseudo-pregnancy in rats. <i>J Physiol</i> , 109(1–2), 17P–21. PMID: 15407435. ³⁴
1949	Parkes AS, & Harris GW (1949). Symposium on neuro-hormonal mechanisms. <i>The J Endocrinol</i> , 6(2). PMID: 15392925
1950	De Groot J, & Harris GW (1950). Hypothalamic control of the anterior pituitary gland and blood lymphocytes. <i>J Physiol</i> , 111(3–4), 335–346. https://doi.org/10.1113/jphysiol.1950.sp004483 . ³⁷
1950	Harris GW (1950). Hypothalamo-hypophysial connexions in the Cetacea. <i>J Physiol</i> , 111(3–4), 361–367. https://doi.org/10.1113/jphysiol.1950.sp004485 PMID: 14795445. ²⁵
1950	Cross BA, & Harris GW (1950). Milk ejection following electrical stimulation of the pituitary stalk in rabbits. <i>Nature</i> , 166(4232), 994–995. https://doi.org/10.1038/166994b0 . ³⁶
1950	Harris GW (1950). Oestrous rhythm. Pseudopregnancy and the pituitary stalk in the rat. <i>J Physiol</i> , 111(3–4), 347–360. https://doi.org/10.1113/jphysiol.1950.sp004484
1950	Colfer HF, De Groot J, & Harris GW (1950). Pituitary gland and blood lymphocytes. <i>J Physiol</i> , 111(3–4), 328–334. https://doi.org/10.1113/jphysiol.1950.sp004482 . ³⁷
1950	Harris GW, & Jacobsohn D (1950). Proliferative capacity of the hypophysial portal vessels. <i>Nature</i> , 165(4204), 854. https://doi.org/10.1038/165854a0 . ⁴¹
1950	Harris GW, & Johnson RT (1950). Regeneration of the hypophysial portal vessels, after section of the hypophysial stalk, in the monkey (Macacus rhesus). <i>Nature</i> , 165(4203), 819–820. https://doi.org/10.1038/165819b0 . ⁴²
1950	Harris GW (1950). The hypothalamus and endocrine glands. <i>Br Med Bull</i> , 6(4), 345–350. https://doi.org/10.1093/oxfordjournals.bmb.a073628 . ⁵⁸
1951	Harris GW (1951). Neural control of the pituitary gland. I. The neurohypophysis. <i>Br Med J</i> , 2(4731), 559–564. https://doi.org/10.1136/bmj.2.4731.559 . ⁵⁶
1951	Harris GW (1951). Neural control of the pituitary gland. II. The adenohypophysis, with special reference to the secretion of A.C.T.H. <i>Br Med J</i> , 2(4732), 627–634. https://doi.org/10.1136/bmj.2.4732.627 . ⁵⁷
1952	Harris GW, & Jacobsohn D (1952). Functional grafts of the anterior pituitary gland. Proceedings of the Royal Society of London. Series B, Biological sciences, 139(895), 263–276. https://doi.org/10.1098/rspb.1952.0011 . ⁴⁷

TABLE 1 (Continued)

Year	Reference
1952	Cross BA, & Harris GW (1952). The role of the neurohypophysis in the milk-ejection reflex. The <i>J Endocrinol</i> , 8(2), 148–161. https://doi.org/10.1677/joe.0080148 . ³⁷
1953	Harris GW The physiology of the hypothalamus and pituitary gland in relationship to gynaecology. <i>Arch Gynak</i> 183, 35–48 (1953). https://doi.org/10.1007/BF01004841 . ⁵⁹
1953	Harris GW, & Pickles, V. R. (1953). Reflex stimulation of the neurohypophysis (posterior pituitary gland) and the nature of posterior pituitary hormone (s). <i>Nature</i> , 172(4388), 1049. https://doi.org/10.1038/1721049a0
1953	Harris GW (1953). The physiology of the hypothalamus and pituitary gland in relationship to gynaecology. <i>Archiv fur Gynakologie</i> , 183, 35–48. https://doi.org/10.1007/BF01004841 . ⁵⁹
1953	Harris GW, & Holton P (1953). Vasodilator activity in extracts of various regions of the central nervous system. <i>J Physiol</i> , 120(1–2), 254–256. https://doi.org/10.1113/jphysiol.1953.sp004890
1954	Donovan BT, & Harris GW (1954). Effect of pituitary stalk section light-induced oestrus in the ferret. <i>Nature</i> , 174(4428), 503–504. https://doi.org/10.1038/174503a0 . ⁴⁴
1954	Harris GW (1954). Recent advances concerning the relationship between the hypothalamus and pituitary gland. <i>Acta Physiol Pharmacol Neerl</i> , 3(2), 289–298. PMID: 13180369
1954	Brown-Grant K, Harris GW, & Reichlin S (1954). The effect of emotional and physical stress on thyroid activity in the rabbit. <i>J Physiol</i> , 126(1), 29–40. https://doi.org/10.1113/jphysiol.1954.sp005189
1954	Brown-Grant K, Harris GW, & Reichlin S. (1954). The influence of the adrenal cortex on thyroid activity in the rabbit. <i>J Physiol</i> , 126(1), 41–51. https://doi.org/10.1113/jphysiol.1954.sp005190
1954	Brown-Grant K, Von Euler C, Harris GW, & Reichlin S. (1954). The measurement and experimental modification of thyroid activity in the rabbit. <i>J Physiol</i> , 126(1), 1–28. https://doi.org/10.1113/jphysiol.1954.sp005188
1955	Donovan BT, & Harris GW. (1955). Neurohumoral mechanisms in reproduction. <i>Br Med Bull</i> , 11(2), 93–97. https://doi.org/10.1093/oxfordjournals.bmb.a069482
1955	Harris GW. (1955). Pituitary–hypothalamic mechanisms. <i>AMA Arch Neurol</i> , 73(2), 124–126. https://doi.org/10.1001/archneurpsyc.1955.02330080002002 . ⁶⁰
1955	Harris GW. (1955). The function of the pituitary stalk. <i>Bulletin of the Johns Hopkins Hospital</i> , 97(5), 358–375. PMID: 13269997. ⁶¹
1956	Donovan BT, & Harris GW. (1956). Adrenergic agents and the release of gonadotrophic hormone in the rabbit. <i>J Physiol</i> , 132(3), 577–585. https://doi.org/10.1113/jphysiol.1956.sp005550
1956	Donovan BT, & Harris GW. (1956). The effect of pituitary stalk section on light-induced oestrus in the ferret. <i>J Physiol</i> , 131(1), 102–114. https://doi.org/10.1113/jphysiol.1956.sp005447 . ⁴⁵
1956	Harris GW., & Woods JW. (1956). Aetiology of Graves's disease in relation to recent experimental findings. <i>Br Med J</i> , 2(4995), 737–739. https://doi.org/10.1136/bmj.2.4995.737
1956	Harris GW., & Woods JW. (1956). Electrical stimulation of the hypothalamus and thyroid activity. <i>Nature</i> , 178(4524), 80–81. https://doi.org/10.1038/178080a0
1956	Harris GW. (1956). Hypothalamic regulation of anterior pituitary secretion. <i>Schweizerische medizinische Wochenschrift</i> , 86(44), 1252–1255.
1956	Taurog A, Harris, GW, Tong W, & Chaikoff IL. (1956). The uptake of I 131-labeled thyroxine and triiodothyronine by the neurohypophysis. <i>Endocrinology</i> , 59(1), 34–47. https://doi.org/10.1210/endo-59-1-34
1957	Campbell HJ, & Harris GW. (1957). The volume of the pituitary and median eminence in stalk-sectioned rabbits. <i>J Physiol</i> , 136(2), 333–343. https://doi.org/10.1113/jphysiol.1957.sp005764
1957	Donovan, BT, & Harris GW. (1957). Pituitary and adrenal glands. <i>Annu Rev Physiol</i> , 19, 439–466. https://doi.org/10.1146/annurev.ph.19.030157.002255
1957	Fortier C, Harris, GW, & McDonald, IR (1957). The effect of pituitary stalk section on the adrenocortical response to stress in the rabbit. <i>J Physiol</i> , 136(2), 344–363. https://doi.org/10.1113/jphysiol.1957.sp005765 . ⁴⁶
1957	Brown-Grant K, Harris GW, & Reichlin, S (1957). The effect of pituitary stalk section on thyroid function in the rabbit. <i>J Physiol</i> , 136(2), 364–379. https://doi.org/10.1113/jphysiol.1957.sp005766
1958	Harris GW (1958). The central nervous system, neurohypophysis and milk ejection. <i>Proc R Soc Lond B Biol Sci</i> , 149(936), 336–353. https://doi.org/10.1098/rspb.1958.0074
1958	Harris GW, & Woods, J. W. (1958). The effect of electrical stimulation of the hypothalamus or pituitary gland on thyroid activity. <i>J Physiol</i> , 143(2), 246–274. https://doi.org/10.1113/jphysiol.1958.sp006057
1960	Campbell HJ, George, R., & Harris, G. W. (1960). The acute effects of injection of thyrotrophic hormone or of electrical stimulation of the hypothalamus on thyroid activity. <i>J Physiol</i> , 152(3), 527–544. https://doi.org/10.1113/jphysiol.1960.sp006507
1960	Harris GW (1960). Central nervous control of gonadotrophic and thyrotrophic secretion. <i>Acta Endocrinol. Supplementum</i> , (Suppl 50), 15–20. https://doi.org/10.1530/acta.0.xxivs015

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TABLE 1 (Continued)

Year	Reference
1962	Harris GW (1962). Neuroendocrine relations. Research publications - Association for Research in Nervous and Mental Disease, 40, 380–405.
1964	Harris GW (1964). Sex hormones, brain development and brain function. <i>Endocrinology</i> , 75, 627–648. https://doi.org/10.1210/endo-75-4-627
1964	Harris GW, & Michael RP (1964). The activation of sexual behaviour by hypothalamic implants of oestrogen. <i>J Physiol</i> , 171(2), 275–301. https://doi.org/10.1113/jphysiol.1964.sp007377
1964	Harris GW (1964). The central nervous system and the endocrine glands. <i>Triangle; The Sandoz Journal of Medical Science</i> , 7, 242–251.
1964	Harris, GW (1964). The development of ideas regarding hypothalamic-releasing factors. <i>Metabolism</i> , 13, 1171–1176. https://doi.org/10.1016/s0026-0495(64)80034-2
1964	Campbell, HJ, Feuer, G, & Harris, GW. (1964). The effect of intrapituitary infusion of median eminence and other brain extracts on anterior pituitary gonadotrophic secretion. <i>J Physiol</i> , 170(3), 474–486. https://doi.org/10.1113/jphysiol.1964.sp007344
1964	Harris GW, Levine S, & Schindler WJ. (1964). Vasopressin and thyroid function in the rat: the effect of oestrogens. <i>J Physiol</i> , 170(3), 516–523. https://doi.org/10.1113/jphysiol.1964.sp007346
1965	Harris GW. (1965). Entwicklung und heutiger stand der neuroendokrinologie [development and present status of neuroendocrinology]. <i>Dtsch Med Wochenschr</i> (1946), 90, 61–65. https://doi.org/10.1055/s-0028-1111294
1965	Harris GW, & Levine S. (1965). Sexual differentiation of the brain and its experimental control. <i>J Physiol</i> , 181(2), 379–400. https://doi.org/10.1113/jphysiol.1965.sp007768
1966	Harris GW, Reed M, & Fawcett CP (1966). Hypothalamic releasing factors and the control of anterior pituitary function. <i>Br Med Bull</i> , 22(3), 266–272. https://doi.org/10.1093/oxfordjournals.bmb.a070485
1967	Harris GW (1967). Elaboration et excrétion des hormones gonadostimulantes. Introduction [Production and excretion of gonadostimulant hormones. Introduction]. <i>Archives d'anatomie microscopique et de morphologie expérimentale</i> , 56(3), 385–389.
1968	Dewhurst KE, el-Kabir DJ, Harris GW, & Mandelbrote DM. (1968). A review of the effect of stress on the activity of the central nervous-pituitary-thyroid axis in animals and man. <i>Confin Neurol</i> , 30(3), 161–196.
1968	Dewhurst KE, Kabir DJ., Exley D., Harris GW., & Mandelbrote, B. M. (1968). Blood-levels of thyrotrophic hormone, protein-bound iodine, and cortisol in schizophrenia and affective states. <i>Lancet</i> , 2(7579), 1160–1162. https://doi.org/10.1016/s0140-6736(68)91639-5
1968	Exley D, Gellert RJ., Harris GW., & Nadler RD. (1968). The site of action of 'chlormadinone acetate' (6-chloro-delta 6-dehydro-17 alpha-acetoxypregesterone) in blocking ovulation in the mated rabbit. <i>J Physiol</i> , 195(3), 697–714. https://doi.org/10.1113/jphysiol.1968.sp008483
1968	Fawcett CP, Reed M, Charlton, HM, & Harris GW (1968). The purification of luteinizing-hormone-releasing factor with some observations on its properties. <i>Biochem J</i> , 106(1), 229–236. https://doi.org/10.1042/bj1060229
1969	Dewhurst KE, El Kabir, DJ, Harris, GW, & Mandelbrote BM (1969). Observations on the blood concentration of thyrotrophic hormone (T.S.H.) in schizophrenia and the affective states. <i>Br J Psychiatry</i> , 115(526), 1003–1011. https://doi.org/10.1192/bjp.115.526.1003
1969	Harris GW., Manabe Y, & Ruf KB (1969). A study of the parameters of electrical stimulation of unmyelinated fibres in the pituitary stalk. <i>J Physiol</i> , 203(1), 67–81. https://doi.org/10.1113/jphysiol.1969.sp008850
1969	Harris GW (1969). Ovulation. <i>Am J Obstet Gynecol</i> , 105(5), 659–669. https://doi.org/10.1016/0002-9378(69)90002-7
1969	Harris, GW, & Sherratt RM (1969). The action of chlormadinone acetate (6-chloro-delta6-dehydro-17alpha-acetoxypregesterone) upon experimentally induced ovulation in the rabbit. <i>J Physiol</i> , 203(1), 59–66. https://doi.org/10.1113/jphysiol.1969.sp008849
1969	Whitteridge D, & Harris, GW (1969). Royal Commission on Medical Education. <i>Lancet</i> , 1(7584), 48. https://doi.org/10.1016/s0140-6736(69)91003-4
1970	Anderson, RM, Harris, GW, DeFilippi, RP, Weber DC, Malchesky, PS., & Nosé, Y (1970). A liquid-liquid contactor for extracorporeal blood oxygenation. <i>Trans Am Soc Artif Intern Organs</i> , 16, 375–380.
1970	Bayman IW, Harris, GW, & Naftolin, F. (1970). Bio-radioimmunoassay of luteinizing hormone releasing factor using untreated immature rats. <i>J Physiol</i> , 210(1), 3P–4P.
1970	Fink G, & Harris, GW (1970). The luteinizing hormone releasing activity of extracts of blood from the hypophysial portal vessels of rats. <i>J Physiol</i> , 208(1), 221–241. https://doi.org/10.1113/jphysiol.1970.sp009115
1970	Harris GW (1970). Effects of the nervous system on the pituitary-adrenal activity. <i>Prog Brain Res</i> , 32, 86–88.
1970	Harris GW (1970). Hormonal differentiation of the developing central nervous system with respect to patterns of endocrine function. <i>Philos Trans R Soc B: Biol Sci</i> , 259(828), 165–177. https://doi.org/10.1098/rstb.1970.0056
1970	Harris GW, & Ruf KB (1970). Luteinizing hormone releasing factor in rat hypophysial portal blood collected during electrical stimulation of the hypothalamus. <i>J Physiol</i> , 208(1), 243–250. https://doi.org/10.1113/jphysiol.1970.sp009116 . ⁵⁵
1970	Harris GW (1970). Structure and function of the median eminence. <i>Am J Anat</i> , 129(2), 245–246. https://doi.org/10.1002/aja.1001290212
1970	Harris GW, & Naftolin F (1970). The hypothalamus and control of ovulation. <i>Br Med Bull</i> , 26(1), 3–9. https://doi.org/10.1093/oxfordjournals.bmb.a070739

TABLE 1 (Continued)

Year	Reference
1970	Harris GW, Anderson, RM, DeFilippi, RP, Nosé Y, Weber DC, & Malchesky PS (1970). The physiological effects of fluorocarbon liquids in blood oxygenation. <i>J Biomed Mater Res</i> , 4(3), 313–339. https://doi.org/10.1002/jbm.820040305
1971	Harris GW (1971). Coordination of the reproductive processes. <i>J Biosoc Sci. Supplement</i> , (3), 5–12. https://doi.org/10.1017/s0021932000023634
1971	Naftolin F, Harris GW, & Bobrow M (1971). Effect of purified luteinizing hormone releasing factor on normal and hypogonadotrophic anovulatory men. <i>Nature</i> , 232(5311), 496–497. https://doi.org/10.1038/232496a0
1972	Cahill GF, Jr, Soeldner JS, Harris GW, & Foster RO (1972). Practical developments in diabetes research. <i>Diabetes</i> , 21(2 Suppl), 703–712. https://doi.org/10.2337/diab.21.2.s703
1972	Harris GW (1972). Humours and hormones. <i>J Endocrinol</i> , 53(2), 2–23.

evident after stimulation of the perivaginal region in the absence of mating and sperm. Each model provides a fabulous system for understanding how external stimulation can produce changes in hormone secretion.^{12,28} Harris's research along these lines inevitably led him to the hypothesis that neural secretions modulated hormone secretions of anterior pituitary control. As noted by Fink in his review, the idea had been suggested previously.^{29,30} Although Harris was not the first to support this idea, he spent much of his research career performing experiments to study the underlying mechanisms and published prolifically.

2.3 | Development of techniques

To study the mechanisms producing ovulation and pseudopregnancy in these models, Harris developed a technique for electrically stimulating the hypothalamic–hypophyseal region through indwelling electrodes in alert unanaesthetized rabbits.^{12,31,32} He applied these methods to studies of both the anterior and posterior pituitary. With his collaborators, Harris was able to activate the hypophysis or the pituitary gland and record a myriad of responses, including water balance, oestrous and ovulation, milk ejection, stress, and gastric motility.^{33–39} It is clear in the discussion section of these empirical studies that Harris was always open-minded about the mechanisms that might mediate these responses. Even in his earliest work, he carefully considered a number of options on how the anterior and posterior pituitary are regulated by the hypothalamus. For example, in 1937, he opined several possibilities.¹²

(1) “That impulses pass along sympathetic fibres in the superior cervical ganglion and carotid plexus ... the sympathetic system plays some part in this mechanism, but presumably not a very large part”; (2) “... That there are sympathetic fibres from the central nervous system which supply the pituitary gland ... There appears to be no experimental evidence put forward for or against this theory”; and (3) “there occurs a humoral or nervous transmission of stimuli from the posterior to the anterior pituitary ... The evidence for this has been mainly of a negative character.”

Almost a decade later, Harris was still mulling over the problem and suggested that there might be a vascular pathway between the hypothalamus and anterior lobe of the pituitary gland.⁴⁰

“It is possible that hypothalamic nerve fibres, ending on the upper set of capillaries in the median eminence, liberate some chemo-transmitter into the portal vessels which is carried humorally to the anterior pituitary and thereby controls or modifies the activity of this gland. Since this mode of control would involve a nervous and vascular link, it has been referred to as ‘neurovascular’ control of the anterior pituitary.”

2.4 | The role of vascular signals

An important line of Harris's research involved the difficult task of determining the contribution of the portal vasculature to the functions he studied. To do this, he cut the blood vessels of the pituitary stalk. He showed that, after severance of the pituitary stalk, the function of the anterior pituitary gland could be correlated with the degree of its revascularization by the hypophyseal portal vessels⁴¹ regeneration in rat⁴² and monkey.⁴³ He also showed that initial loss of function of several different pituitary responses could be restored following pituitary stalk transection, possibly as a result of this revascularization mechanism.^{44–46}

2.5 | Transplant studies

Another direction that addressed vascularization involved the study of pituitary transplants. In this work, Harris showed that the morphological and functional integrity of pituitary grafts were maintained when these grafts were vascularized by the hypophyseal portal but not by the systemic circulation.^{47,48} As an example of his thorough approach, four strategies were tried in one such experiment: (1) Hypophysectomy and transplantation of anterior lobe – tissue under the median eminence; (2) hypophysectomy and transplantation of the extirpated anterior lobe into the emptied hypophyseal capsule; (3) extirpation of the anterior pole of the hypophysis; and (4) section of the hypophyseal stalk.⁴¹

2.6 | The direction of blood flow

Although the foregoing work was suggestive, direct evidence on whether the flow of information was from the brain to the pituitary or vice versa was much more difficult to establish and remained controversial for decades.⁴⁹ To start, Popa and Fielding suggested that blood flowed upwards, from the pituitary gland to the hypothalamus, asserting "...That the blood flows in these vessels in the direction stated [from pituitary to hypothalamus] is evident from their colloid accompaniment." Harris and Green, however, demonstrated definitively that the direction of blood flow in the portal vessels of living rats was from the hypothalamus to the pituitary,⁵⁰ as had already been shown in *Bufo arenarum* and *Rana catesbiana* by Houssay et al.⁵¹ and Green.⁵² It remained to be demonstrated that chemical substances of neural origin actually flowed within these vessels. Of course, the identity of the neurosecretions in this system was established by the 1977 Nobel Prize-winning work of Guillemin and Schally.^{53,54} Not surprisingly, Harris also pursued these questions.⁵⁵ In summary, as documented in a lovely review by Watts,²¹ the experimental work of Harris and his colleagues has stood the test of time. This is evident in a steady increase in the resolution and identification of mechanisms demonstrating the hypothalamic loci of neurosecretory neurons, the identity of neurosecretions of the hypothalamus, and their relationships to the pituitary secretions.

2.7 | Literature reviews

In addition to performing many multifaceted empirical studies, Harris published a steady stream of reviews. Over the years, he fine-tuned his understanding of the portal system and steadily documented his developing ideas.^{56–61} Harris's 1955 book was the culmination of his careful analysis and his ability to integrate myriad studies and ideas — both his own and those of others. Harris's vision in this book was based on a careful, critical summary of the literature demonstrating a vascular portal pathway from the hypothalamus to the pituitary. The book was very well received, as can be seen in a review by Mary Pickford.⁶²

"The subject has an enormous literature, and Professor Harris has done well to compress his account into less than 300 pages. He has achieved this partly by cutting down the list of references to the more important ones, and partly by presenting the point of view which seems to him most likely to be found true in the light of later work. Though some people here and there may disagree with his opinions, this method of presentation is far more stimulating than an indiscriminating summary of all the literature."

Retrospectively, Harris is generally credited with founding the field of Neuroendocrinology. In Harris's lifetime, however, the situation was more fraught, as documented by Seymour Reichlin.¹⁸ Harris

was criticized for years by Sir Solly Zuckerman, a prestigious Professor of Anatomy at the University of Birmingham. Zuckerman dismissed Harris's theory about the role of the pituitary portal vessels in anterior pituitary regulation.^{20,63} Zuckerman's experiments appeared to demonstrate that female ferrets bearing a cut pituitary stalk came into heat in the absence of portal vessel connections, as shown by Indian ink vascular perfusion.⁶⁴ In the honest ways of science, Reichlin reports that Harris was permitted to examine the brains of these ferrets and found that their portal blood vessels had regenerated. Additionally, Donovan and Harris⁴⁴ repeated the study with somewhat improved methods and confirmed their own conclusions. Zuckerman was unconvinced of Harris's interpretation and stubbornly retained his doubts for decades.^{20,65,66}

3 | THE SCN-OVLT CONNECTION: IDENTIFICATION OF A SECOND PORTAL PATHWAY IN THE BRAIN

Almost 100 years after Popa and Fielding described the pituitary portal system, we discovered a second portal pathway in the mouse brain.⁴ A possible reason that the SCN-OVLT pathway was not seen in previous studies is that both structures lie in the midline, and the connecting capillaries lie on the floor of the third ventricle. These connections tend to be damaged when preparing brain sections. We used brain clearing methods, immunochemistry, and light sheet microscopy, enabling 3D reconstruction of the area. Figure 3 shows the images one can glean from the classical methods compared to the methods possible today.

Anatomical evidence constitutes the necessary infrastructure to explore brain function. Demonstrating a link between the capillary vessels of the brain's clock in the SCN and those of a circumventricular organ (CVO), the OVLT, is a first step in exploring this communication pathway. The SCN is a hypothalamic nucleus known as the brain's circadian clock: it is found in all vertebrates that have been studied.⁶⁷ The OVLT is a sensory CVO with fenestrated blood vessels, and it is best known for its role in regulating thirst and water balance, among other functions.^{68–70} The local connections between blood vessels of the SCN-OVLT, similar to those of the pituitary portal pathway, enable small amounts of neurosecretions to reach their specialized targets in high concentrations without dilution in the general circulatory system. Although the anatomical work reported to date did not establish the direction of blood flow, we conjectured that blood flows from the SCN to the OVLT based on a host of prior studies and on our substantial knowledge of the SCN⁴ (Figure 4).

The establishment of a significant function of the SCN-OVLT portal systems in the brain is likely to be challenged, as was the work of Harris. Hopefully, the road toward establishment will not involve the personally directed hostility faced by Harris. That said, there is no question that the pituitary portal system is not the only one in the brain. The long series of studies required to prove significant functions of the SCN-OVLT portal connections have just begun, and the major landmarks in our understanding are parallel to those of Harris

SCN-OVLT portal system: 90 years after Popa & Fielding

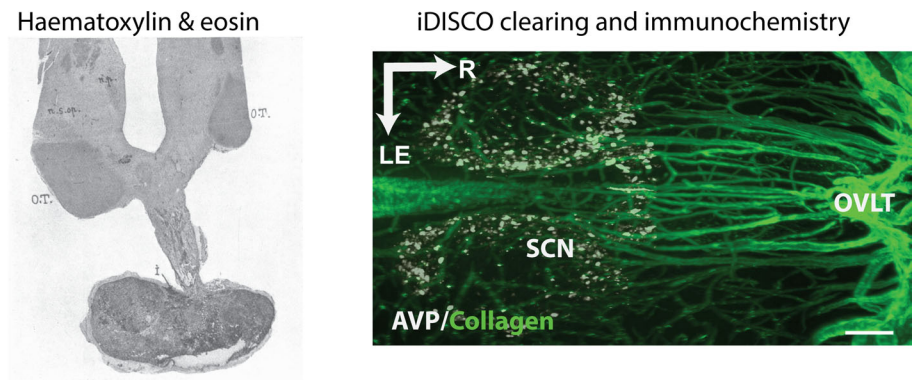


FIGURE 3 One portal pathway links median eminence to the pituitary gland, while another links the suprachiasmatic nucleus (SCN) to the organum vasculosum of the lamina terminalis (OVLT). The image on the left shows the hematoxylin and eosin stain. From “Hypophysis-portal vessels and their colloid accompaniment” by Popa and Fielding (1933).² The image on the right shows an iDisco cleared mouse brain stained with arginine vasopressin (AVP) to identify SCN and collagen to label blood vessels.⁴ Today’s tools permit not only a finer depiction of these blood vessels but also more certainty about their anatomical features. LE, left; R, rostral. Scale bar = 100 μm.

FIGURE 4 Detailed sagittal view of suprachiasmatic nucleus (SCN)-organum vasculosum of the lamina terminalis (OVLT) portal vessels. The suprachiasmatic nucleus (SCN) is labeled by arginine vasopressin (AVP) and the OVLT is delineated by its characteristic loopy blood vessels (see text). LE, left; R, rostral. Scale bar = 150 μm.

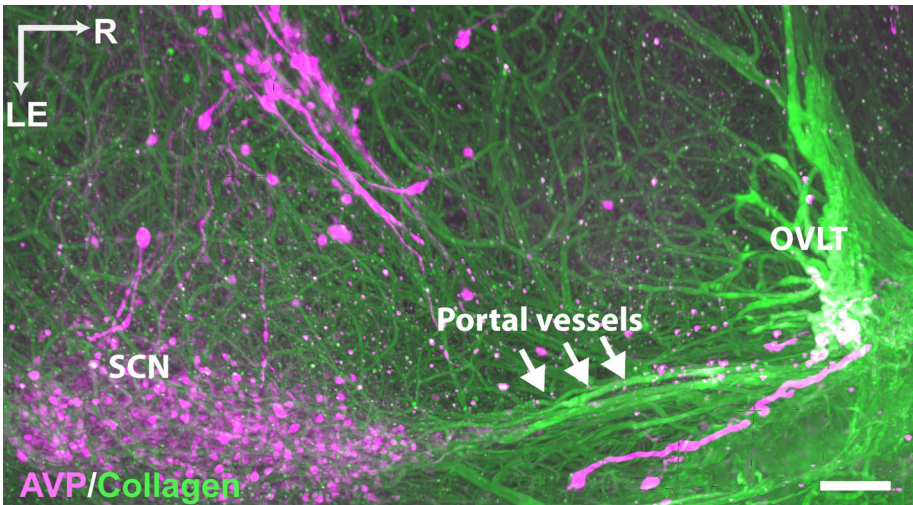


TABLE 2 Parallel trajectories in studies of pituitary and SCN-OVLT portal pathways.

Pituitary portal system	SCN-OVLT portal system
• 1930: Anatomy – rat portal system	• 2021: Anatomy – mouse portal system²
• 1952: Transplants of the pituitary	• 1987–1996: Transplants of the suprachiasmatic nucleus^{1,4}
• 1930–1955: Direction of blood flow	• 2022: Direction of blood flow (current work)
• 1972: Identification of “chemical neurosecretions” releasing hormones	• 2022: Hypothesis: Identification of “chemical neurosecretion” as arginine vasopressin from the SCN

(Table 2). In the case of the pituitary portal system, it took from 1930 to 1955 to achieve reasonable consensus on the importance of this communication pathway and another two decades to begin to identify

the chemical secretions carried in this system. In the case of the SCN-OVLT, newer tools enable more definitive studies and, hopefully, faster progress.

3.1 | SCN transplants provide evidence of a humoral output signal

The SCN was first identified as a master circadian clock in the brain in the early 1970s.^{71,72} That initial work has been supported by empirical and modeling research in the following decades.^{73–77} Much work in many different labs indicated that transplants of the SCN tissue into an SCN-ablated host restored circadian rhythms.^{78–81} However, several years of experimental work failed to reveal a necessary neural connection between the donor tissue and the host brain.^{82–85} Direct evidence that the SCN produces a diffusible signal is based on transplant studies in which the nucleus was encapsulated in a copolymer

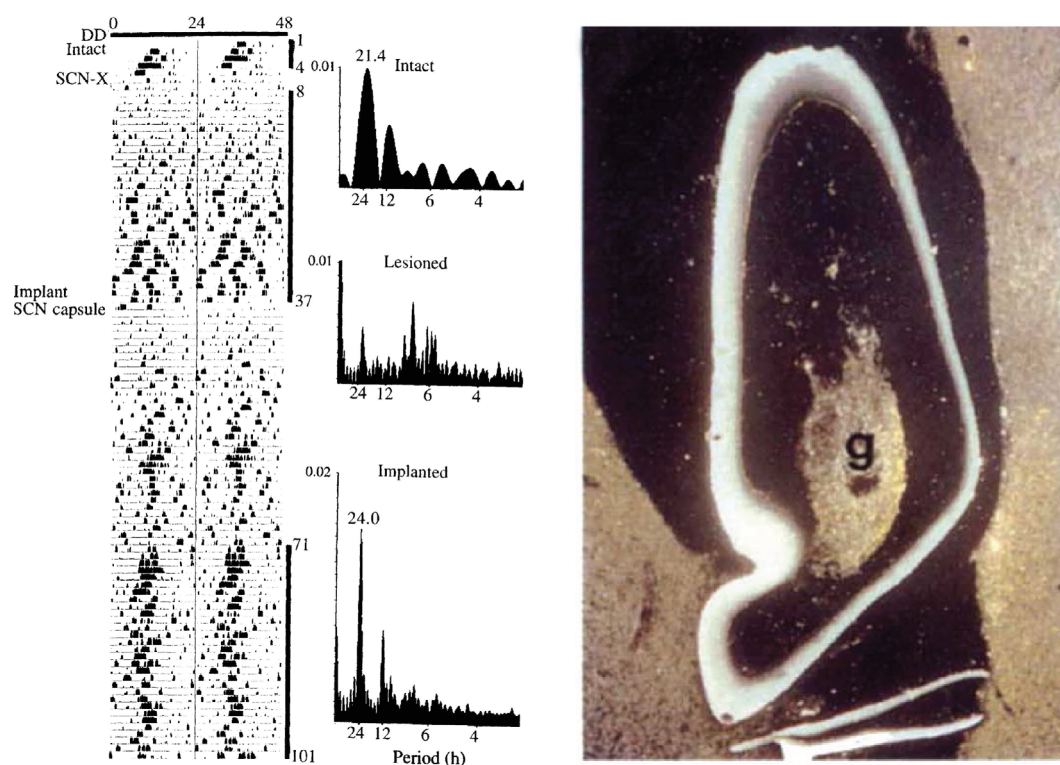


FIGURE 5 The work depicted here proves that a humoral signal from the suprachiasmatic nucleus (SCN) can sustain circadian locomotor rhythms. Left: An actogram of an intact mutant animal with an approximately 21.4-h free-running locomotor rhythm after it received an SCN lesion and following implantation of an encapsulated SCN from a wild-type donor animal with an approximately 24-h endogenous rhythm. The Fourier analysis shows the quantification of the free-running behavior. Right: The encapsulated grafted SCN tissue. From “A diffusible coupling signal from the transplanted suprachiasmatic nucleus controlling circadian locomotor rhythms” by Silver et al. (1996).⁸⁶ DD, constant darkness; g, SCN grafts; SCN-X, SCN-lesioned.

membrane and placed in the third ventricle of an animal whose own SCN had been ablated.⁸⁶ The encapsulated graft permitted the diffusion of molecules but eliminated the possibility of fiber outgrowth. In this study, the grafted tissue was taken from donor wild-type hamsters that had a typical free-running period of 24 h and implanted into mutant hamsters hosts that had a (on average) free-running period of approximately 20 h.⁸⁷ The recovered period was that of the donor tissue. This experiment provided definitive proof that a humoral signal could support circadian rhythms of locomotor activity (Figure 5).

3.2 | Functions restored by humoral signals

Importantly, transplants of the SCN restore behavioral rhythmicity such as locomotor, drinking, and gnawing rhythms but do not restore endocrine rhythms.⁸⁸ A number of diffusible signals have been implicated as output signals of the SCN.^{89–91} It remains to be determined which of these chemical messengers travel via the portal system to modulate the responses supported by SCN transplants. Once identified, it will be necessary to document the role played by the portal system. Although the identity of the chemical messenger that might travel in the SCN-OVLT portal pathway is unknown, it is nevertheless important to ask what part of this complex CVO can receive this input.

3.3 | Characteristics of CVOs

CVOs comprise a group of vascularized regions protruding into the ventricles. Although little is known about the developmental and evolutionary origins of the CVOs, they are divided into two categories: secretory or sensory.⁹² The secretory CVOs include the median eminence, neurohypophysis, pineal gland, and subcommissural organ. The sensory CVOs include the OVLT, subfornical organ, and area postrema. The vasculature of the CVOs (except the subcommissural organ) is characterized by fenestrated capillaries and large perivascular spaces.^{93,94} Because they provide access to the interstitial spaces of the brain, CVOs have been characterized as “windows to the brain.”⁹⁵ We hypothesize that humoral signals from the SCN course along portal capillaries to the leaky vessels of the OVLT. From here, such signals can reach the cerebrospinal fluid and interstitial spaces deep within the brain.

3.4 | OVLT boundaries

The OVLT is located near the ventral aspect of the anterior wall of the third ventricle. Several methods have been used to delineate its borders, with similar findings obtained using various methods.^{96–98} As

noted below,⁹⁹ because the fenestrated capillaries of the OVLT allow the passage of the tracers into its interstitium, the nuclear boundaries can be determined by the localization of Evans Blue tracer following intravenous injection.

“... the OVLT is a complex three-dimensional structure. In coronal view, the rostral OVLT is shaped like an inverted heart bordered dorsally by the vertical limbs of the nucleus of the diagonal band of Broca. The ventral surface of the rostral OVLT lies directly above the prechiasmatic cistern that houses the preoptic vascular plexus. The caudal portion of the OVLT is vertically elongated and bordered ventrally by the optic chiasma and dorsally by the median preoptic nucleus. The caudal pole of the OVLT interfaces with the ventral part of the third ventricle, including the small optic recess located directly above the optic chiasma.”

3.5 | The OVLT is a heterogeneous CVO

A thorough overview of the OVLT is available.¹⁰⁰ The nucleus is divided into three subregions, namely a rostromedial, a laterocaudal, and a dorsal region. The first two regions are based on their vasculature features, whereas the dorsal cap covering the top of the OVLT is characterized by its functional aspects. In the rostromedial region, there is a superficial capillary plexus, large perivascular spaces, and neurosecretory terminals. The laterocaudal region includes a deep capillary plexus formed by a few branches exiting the superficial capillary plexus. Distinct afferent and efferent connections of the OVLT subregions have been described.^{101,102} The dorsal cap is highly responsive to hypertonicity. The understanding of the OVLT anatomy has been greatly expanded by depicting the interdigitation of glial elements, including tanyocytes, ependymocytes, and astrocytes, between local neuron populations.⁹⁹ The subdivisions of OVLT and localization of capillary plexi are shown in Figure 6.

3.6 | Characterization of OVLT capillary plexi

The SCN-OVLT portal vessels connect to the OVLT at its base, but we do not yet know the targets of any bloodborne products. There are two major vascular plexi in the OVLT: the superficial plexus in the rostromedial region (also called the primary plexus) and the deep plexus (also called the secondary plexus) in the laterocaudal region, each bearing several distinct features. For example, the density of the blood vessels is different. The superficial plexus has a significantly higher density and more intertwined structure than the deep plexus. They also differ in the size of their perivascular spaces, with large perivascular spaces around the superficial capillary plexus but not the deep plexus.⁹⁴ Finally, the capillary plexi differ in their permeability to tracers; larger tracers, such as dextran 10K, are confined to the perivascular space around the superficial plexus, while smaller tracers,

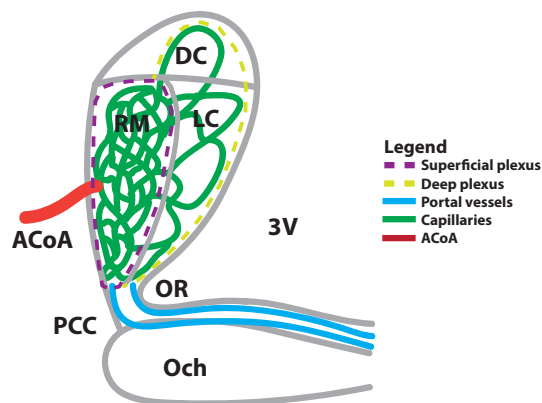


FIGURE 6 The diagram depicts the three compartments of the organum vasculosum of the lamina terminalis (OVLT) in sagittal view. The blood supply to the OVLT derives from the anterior communicating artery (ACoA) and enters the nucleus near the superficial plexus while the portal vessels reach the OVLT at its base. 3V, third ventricle; DC, dorsal cap; LC, laterocaudal region; Och, optic chiasma; OR, optic recess; PCC, prechiasmatic cistern; RM, rostromedial region.

such as fluorescein isothiocyanate or dextran 3K, can penetrate the deep plexus into the subependymal region.¹⁰³

3.7 | Portal vessel–OVLT

It remains to be established whether the portal vessels from the SCN connect to the superficial plexus or deep plexus. The ventral border of the deep capillary protrudes into the optic recess of the third ventricle, whereas the ventralmost part of the superficial plexus enters the floor of the third ventricle below the optic recess. Portal vessels from the SCN travel along the third ventricle floor before joining the OVLT capillaries. Thus, localization of the superficial plexus renders it more accessible to the portal vessels. A notable feature of the ventral part of the superficial plexus is a large number of fibers co-expressing glial fibrillary acidic protein and vimentin.⁹⁹ These fibers suggest that the entry point of portal vessels into the OVLT may have abundant tanyocyte terminals.

4 | DEFINING FEATURES OF NEUROVASCULAR PORTAL SYSTEMS

To the best of our knowledge, there is but one additional mention of a portal pathway in the brain, by Roth and Yamanoto.¹⁰⁴ In their description of the microcirculation of the area postrema it is noted that “... enlarged capillary channels are re-entrant” at the borders of the area postrema, where they are joined by short interconnecting vessels to capillaries of smaller caliber typical of the medullary tissue. They suggest that this may be a portal system because two distinctive, serially connected capillary beds are interposed between the artery and vein (Figure 7). If a portal system is defined as a vascular

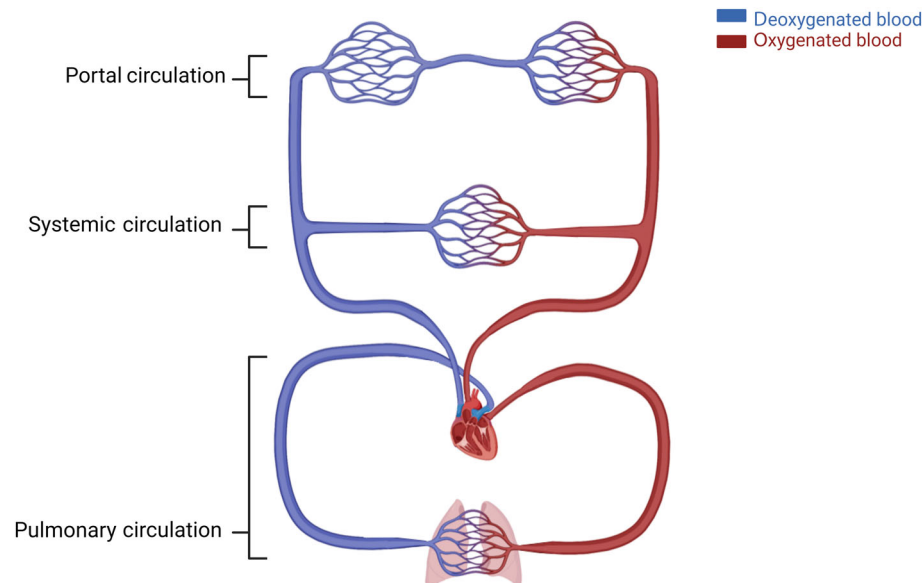


FIGURE 7 Depicting the flow of blood through a portal pathway and in the systemic and pulmonary circulatory systems.

arrangement in which blood from the capillaries of one organ is transported to the capillaries of another organ by a connecting vein or veins. By this definition, only the pituitary portal system and the SCN-OVLT portal systems meet the criterion, while the area postrema-medulla capillary beds do not. However, in a broader view, other categories of joined capillary beds can be considered. As noted by Roth and Yamamoto (1968), the Area Postrema and adjacent medullary capillary beds lack a connecting vessel but share capillary vessels fenestrated and non-fenestrated respectively. As such they do not meet the common definition of a portal system, yet the sharing of capillary beds provides a mechanism for neural secretions to reach specialized local targets. Immediately obvious is the fact that the three portal systems under discussion have both common and unique features. Common to all three systems is the idea that the shared vascular capillary beds provide a route for anatomically/morphologically distinct structures to share neurochemical secretions. That said, the pituitary portal system connects the leaky fenestrated capillaries of the median eminence and the pituitary gland. The SCN-OVLT portal pathway connects the non-fenestrated capillary vessels of the SCN to the fenestrated vessels of the OVLT. The area postrema and medulla capillary beds are joined directly and lack connecting capillary veins.

5 | FUTURE DIRECTIONS

As stated above, once the pituitary portal pathways had been anatomically identified, major challenges remained, and the same landmarks to discovery are needed to understand the SCN-OVLT system. These include (1) determination of the direction of flow; (2) the source(s) and target(s) of information transfer; (3) identification of the signals flowing in these pathways; and (4) determination of the specific function of those signals. Although it took several decades to address these critical challenges for the hypothalamic-pituitary portal system, we anticipate that recent molecular, genetic, and technological advances

will hasten these answers in the case of the recently discovered SCN-OVLT portal system. Several precedents point to tools and available methods.

For the pituitary portal system, Green and Harris were able to visualize the blood vessels linking the median eminence of the hypothalamus and anterior pituitary because the portal vessels exit the bony base of the brain and are relatively long. We recently implemented an innovative experimental procedure¹⁰⁵ in which we combined two-photon imaging in transgenic rats expressing an arginine vasopressin-enhanced green fluorescent protein fusion gene¹⁰⁶ along with a transpharyngeal surgical procedure. This toolbox enabled us to expose and image the ventral hypothalamus, studying for the first time in vivo neurovascular responses and changes in blood flow in the hypothalamus within the bony base of the brain. In this work, we were able to examine the microvasculature of the supraoptic nucleus (SON) in response to a systemic salt challenge.¹⁰⁵ Using a modified version of this approach, we identified the SCN and its microvasculature (Figure 8; unpublished results by R. K. Roy & J. E. Stern), which will allow us to readily and rapidly determine the directionality of blood flow within this system.

The advent of novel biosensors for detecting a variety of neuropeptides constitutes a promising venue for identifying signals traveling within brain portal systems, including the SCN-OVLT. For example, we and others have used biosensor “sniffer” cells to detect, with extremely high sensitivity and specificity in real time, endogenously-released vasopressin and oxytocin within the SON and SCN.^{107,108}

More recently, biosensors have been genetically expressed and used in conjunction with viral gene delivery. They can also be efficiently employed to monitor the endogenous release, in real time, of various neurotransmitters within the paraventricular nucleus.^{109,110} Thus, biosensors have high sensitivity and specificity, along with the ability to deliver them in a region-specific and even cell-type-specific manner. They stand as efficient candidates to identify and measure signals being released and traveling within the SCN-OVLT portal

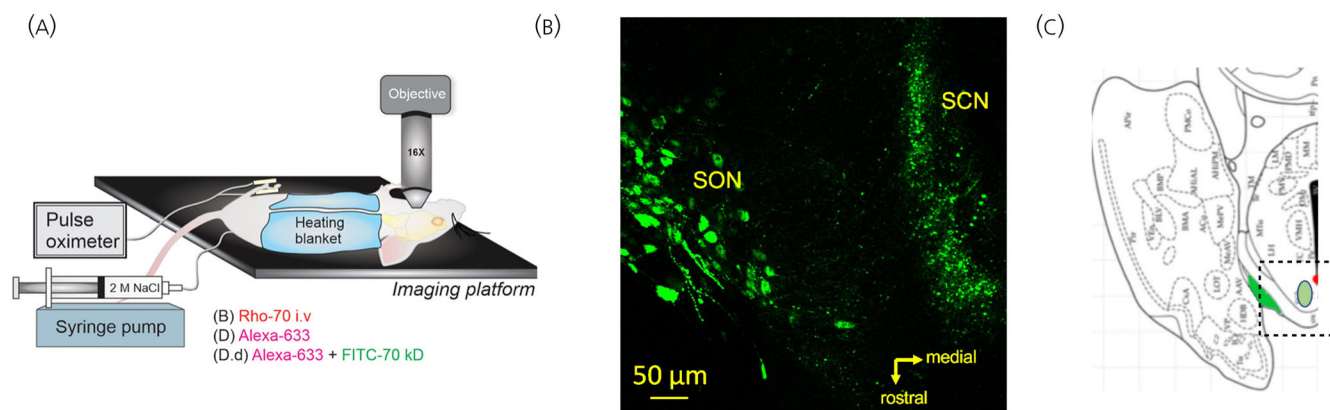


FIGURE 8 In vivo two-photon imaging of the hypothalamic supraoptic (SCN) nucleus in the arginine vasopressin (AVP)-enhanced green fluorescent protein (eGFP) anesthetized rat. (A) Schematic representation of the in vivo preparation used to visualize the supraoptic nucleus (SON) and the SCN using a ventral approach. From “Inverse neurovascular coupling contributes to positive feedback excitation of vasopressin neurons during a systemic homeostatic challenge” by Roy et al. (2021).¹⁰⁵ (B) In vivo two-photon imaging of vasopressin eGFP fluorescence in the SON and SCN. Note the large magnocellular neurons in the SON compared to the SCN (unpublished data by R. K. Roy & J. E. Stern). (C) Schematic representation of the brain region imaged in (B).

system, without the need of using a large number of animals, as was needed in the past to identify and measure signals traveling in the hypothalamic–pituitary portal. As previously noted¹¹¹ “A major boost to Schally’s efforts came from the meat-packer Oscar Mayer and Company, which donated a million pig hypothalami.”

6 | THE LONG VIEW

As these highly sensitive anatomical, molecular, and functional approaches become more readily accessible to the neuroscientific community, we anticipate that other brain portal systems will be unveiled. Thus, rather than being considered a singularity, brain vascular portal systems may be recognized as functionally essential alternative pathways for the transfer of signals and information processing within the brain, having once again, as decades ago, an important impact on the field of Neuroendocrinology.

AUTHOR CONTRIBUTIONS

Rae Silver: Conceptualization; data curation; funding acquisition; project administration; resources; supervision; visualization; writing – original draft; writing – review and editing. **Yifan Yao:** Conceptualization; validation; visualization; writing – original draft; writing – review and editing. **Ranjan Roy:** Visualization. **Javier E Stern:** Funding acquisition; writing – original draft; writing – review and editing.

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study. This is a review article.

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