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Quick guide

The parasubthalamic nucleus

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What is the parasubthalamic nucleus? The parasubthalamic nucleus (PSTN) is a small but functionally important cluster of excitatory neurons located in the posterior hypothalamus (Figure 1A). Despite its modest size, the PSTN plays a critical role in regulating survival behaviors including appetite suppression, aversion, autonomic regulation, and wakefulness. By integrating sensory, hormonal, and emotional signals, the PSTN helps animals adapt their behavior in response to changing internal and external conditions.

Where does the PSTN get its name? The PSTN is named for its anatomical position just medial ('para—') to the subthalamic nucleus (STN). Although often overshadowed by its larger neighbor, the PSTN is distinct in its gene expression, anatomical connections, and behavioral functions. It has sometimes also been referred to as the *posterior* subthalamic nucleus, *medial* subthalamic nucleus, or abbreviated as PSTh in some studies.

Is the PSTN conserved across species? While most research on the PSTN has been conducted in rodents, homologous structures have been identified in non-human primates and humans, suggesting a conserved role across mammals. However, its precise anatomy and molecular profile may differ somewhat between species.

What types of neurons make up the PSTN? All PSTN neurons are excitatory, releasing glutamate to activate downstream targets. Within this population, two principal, non-overlapping subtypes stand out: neurons expressing tachykinin-1 (Tac1) and a smaller subset expressing corticotropin-releasing hormone (CRH) (Figure 1B). Together, these two subtypes account for approximately 80% of PSTN neurons. Other molecular markers, including pituitary adenylate cyclase-activating polypeptide (PACAP), calbindin, calretinin, preproenkephalin, and neurotensin, are also present but are not exclusive to the PSTN, extending beyond its defined borders. Therefore, Tac1 and CRH expression best delineate PSTN neuronal subpopulations.

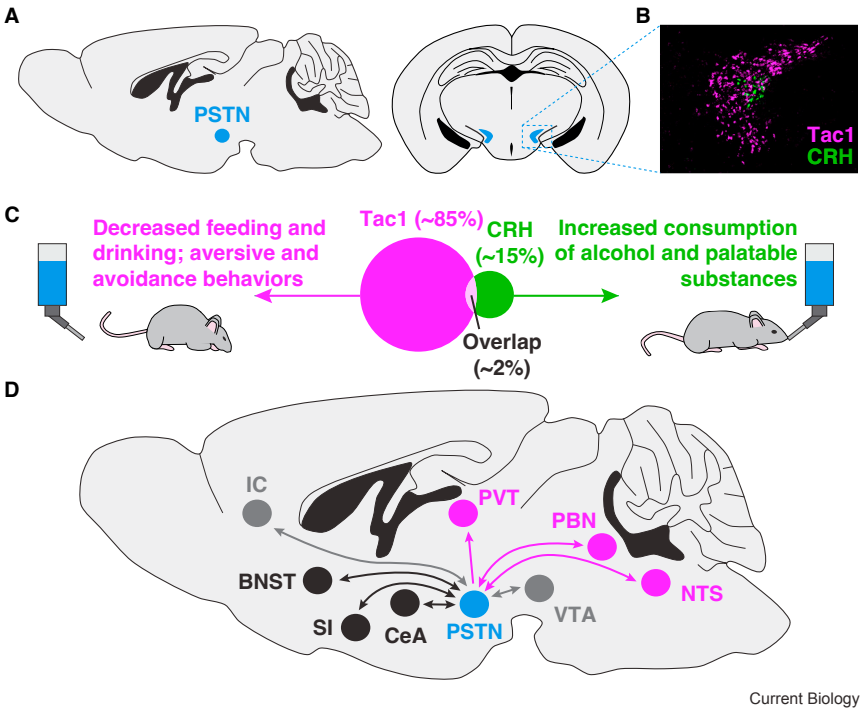

Figure 1. The parasubthalamic nucleus (PSTN).

(A) Sagittal (left) and coronal (right) diagrams showing the location of the PSTN in a rodent brain. (B) Fluorescent *in situ* hybridization image of the PSTN, illustrating Tac1-expressing neurons (magenta) and CRH-expressing neurons (green). (C) Diagram showing the relative percentage of Tac1- versus CRH-expressing neurons within the PSTN and the dominant behaviors each population regulates. (D) Major afferent and efferent projections of the PSTN. Magenta arrows indicate projections specific to Tac1-expressing neurons. BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; IC, insular cortex; NTS, nucleus of the solitary tract; PBN, parabrachial nucleus; PVT, paraventricular thalamic nucleus; SI, substantia inominata; VTA, ventral tegmental area.

What is the role of the PSTN in appetite? One of the PSTN's best-characterized roles is in appetite regulation. Tac1-expressing PSTN neurons become active at the onset of food consumption and in response to stomach distention. They are also engaged by a variety of appetite-suppressing hormones released during digestion, including amylin, cholecystokinin, peptide YY, and GLP-1. Therefore, sensory, neural, and hormonal signals converge to activate the PSTN during feeding.

Experimental stimulation of Tac1-expressing PSTN neurons suppresses food intake, while inhibiting them leads to overeating — even when satiety signals are present. Therefore, these neurons appear to function as internal stop signals, preventing overconsumption in the face of satiety cues (Figure 1C).

Could activating the PSTN help with weight loss? Probably not — at least not in a way that anyone would want. Artificial activation of Tac1-expressing PSTN neurons is aversive: animals avoid environments where PSTN stimulation has occurred. This suggests that the PSTN does more than signal fullness — it likely produces an unpleasant, negative experience when strongly activated.

What about the other aversive functions of the PSTN? Beyond feeding, Tac1-expressing PSTN neurons respond robustly to a range of aversive stimuli, including malaise, pain, and fear. For example, they become active when animals encounter toxins, experience footshocks, or smell predator odors. Silencing these neurons reduces fear-induced freezing and the suppression of feeding in threatening contexts, underscoring their role in linking negative experiences to adaptive behavioral responses.

How can Tac1-expressing PSTN neurons regulate both appetite suppression and aversion? The PSTN is anatomically situated at the intersection of interoceptive signals (such as hunger and fullness) and emotional processing (such as fear and malaise). This position allows it to shift behavioral priorities — for example, suppressing feeding when danger is present. By integrating visceral and emotional inputs, the PSTN helps organisms make survival-driven decisions.

What about CRH-expressing PSTN neurons? Do they have a function? In contrast to Tac1-expressing neurons, CRH-expressing PSTN neurons promote consummatory behaviors. They drive the consumption of alcohol, water (in thirsty animals), and palatable substances like saccharine. These neurons are particularly engaged in models of alcohol use disorder, where chronic intermittent ethanol exposure leads to excessive alcohol intake. Silencing CRH-expressing PSTN neurons reduces this escalation and accelerates recovery from alcohol withdrawal-related pain. Thus, while Tac1 neurons suppress ingestion and promote aversion, CRH neurons facilitate consumption and may contribute to addiction and pain modulation (Figure 1C).

Given their distinct functional roles, do Tac1- and CRH-expressing PSTN neurons connect to different brain regions? They do. Both Tac1- and CRH-expressing PSTN neurons project to limbic structures that regulate motivation and aversion, including the central nucleus of the amygdala (CeA), bed nucleus of the stria terminalis (BNST), and substantia inominata (SI). However, Tac1-expressing neurons uniquely send projections to brain regions that integrate visceral signals and suppress feeding, such as the nucleus of the solitary tract (NTS), parabrachial nucleus (PBN), and paraventricular thalamus (PVT) (Figure 1D). The PSTN also projects to the insular cortex and ventral tegmental area (VTA), although it is not yet clear which specific neuron types are involved.

Interestingly, the PSTN forms bidirectional connections with many of these regions, receiving input and sending projections to the same structures (with the PVT as a notable exception). Through these connections, the PSTN serves as a critical interface between bodily sensations and motivated behaviors. Whether individual PSTN neurons project to multiple downstream targets or to specific areas remains an open question.

Is the PSTN implicated in other behaviors? Yes — in addition to its roles in feeding and aversion, the PSTN promotes wakefulness, particularly arousal associated with exploration. It also influences autonomic regulation by exciting parasympathetic neurons in the NTS, thereby reducing heart rate and blood pressure. Future studies are needed to clarify how Tac1- and CRH-expressing neurons contribute to these additional behaviors.

What's next? Although the PSTN was first described over two decades ago, its essential roles in appetite suppression, aversion, and other survival behaviors have only recently been identified. A key priority moving forward is to map the specific afferent pathways that activate distinct PSTN populations in response to internal and external cues, as well as the efferent projections through which these neurons influence behavior. Given its position as a bidirectional hub (Figure 1D), understanding how upstream activity reverberates through PSTN circuits to influence downstream targets will be crucial. Studying this small but strategically positioned nucleus may yield outsized insights into how the brain balances competing drives with adaptive action.

Where can I find out more?

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DECLARATION OF INTERESTS

The author declares no competing interests.

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