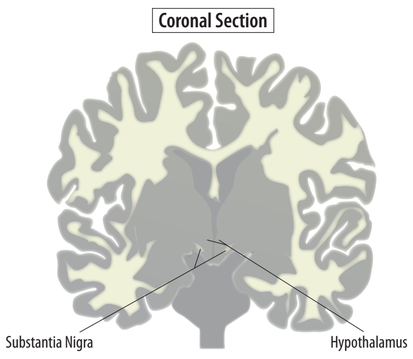
Neurotransmitter Receptors in the Substantia Nigra & the Tuberomammillary Nucleus

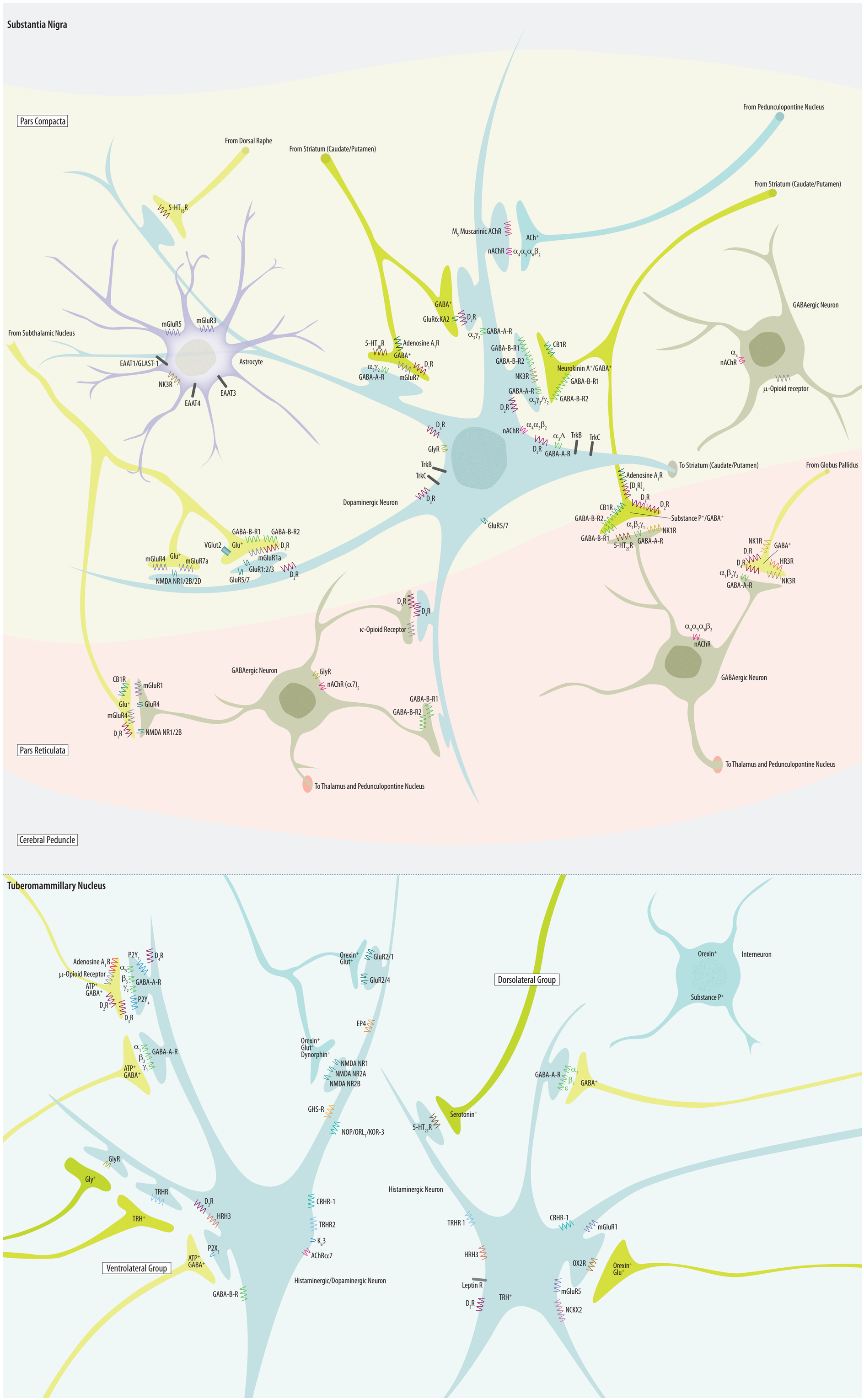


The Substantia Nigra

The substantia nigra (SN) is an area of deeply pigmented cells in the midbrain that regulates movement and coordination. Neurons of the SN are divided into the substantia nigra pars compacta (SNc) and the substantia nigra pars reticulata (SNr). Neurons of the SNc produce Dopamine, which stimulates movement. In contrast, GABAergic neurons of the SNr can stimulate or inhibit movement depending on the input signal.

The SN controls movement by functioning as part of the basal ganglia, a network of neurons that is critical for motion and memory. Along with the SN, the basal ganglia consists of the putamen, the subthalamic nucleus, the caudate, and the globus pallidus, which is further divided into the globus pallidus interna (GPi) and the globus pallidus externa (GPe). Excluding the caudate, which is thought to be involved in learning and memory, the nuclei of the basal ganglia receive signals from the cerebral cortex when there is intent to coordinate movement. Signals received by the basal ganglia from the cerebral cortex can be relayed through a direct pathway, which may stimulate movement, or an indirect pathway, which may inhibit movement. In the direct pathway, inhibitory outputs project directly from the putamen to the SNr or GPi, which transmit inhibitory signals to the thalamus. In response, the thalamus sends excitatory signals back to the cerebral cortex, which leads to the modulation of motor neurons. In the indirect pathway, signals are relayed from the putamen to the GPe prior to reaching the SNr/GPi. The presence of the extra step in the indirect pathway reduces thalamic activity, which is thought to downregulate movement. The combined actions of signals transmitted via the direct and indirect pathways are believed to enable fine movement control.

Dopamine produced by the SNc and Acetylcholine produced by cholinergic interneurons affect movement through interactions with the direct and indirect pathways. Acetylcholine inhibits movement by exciting the indirect pathway and inhibiting the direct pathway. In contrast, Dopamine increases movement by stimulating the direct pathway (Dopamine 1 Receptor-mediated) and inhibiting the indirect pathway (Dopamine 2 Receptor-mediated). Degeneration of dopaminergic neurons, a hallmark of Parkinson's disease, leads to a significant reduction in neuronal Dopamine, which reduces excitation of the direct pathway and increases the activity of the indirect pathway. Thus, the loss of Dopamine causes an imbalance of activity in the direct:indirect pathways, which causes a net loss of motor activity and a reduction in fine movement control.



The Tuberomammillary Nucleus

Located in the posterior hypothalamus, the tuberomammillary nucleus (TMN) is a compact cluster of neurons that serves as the sole source of neuronal Histamine. Although small in size, the TMN regulates several biological processes including thermoregulation, food intake, neuroendocrine functions, and the sleep-wake cycle. Its role in the sleep-wake cycle is supported by the observation that TMN activity is highest during wakefulness, low during slow wave (deep) sleep, and absent during REM sleep. Activity of TMN neurons is also influenced by inputs from GABA-, Orexin/Glutamate-, and endocannabinoid-expressing neurons.

Histamine, produced by decarboxylation of Histidine, is released at sites that lack classical synapses, appears to diffuse freely, and has no high-affinity uptake mechanism. Extracellularly, Histamine can be inactivated by neuronal Histamine N-Methyltransferase or it can bind to Histamine Receptors expressed by nearby neurons. Histamine Receptors differ in localization, function, and signaling properties depending on the receptor subtype. For example, Histamine H1 Receptors (HRH1), HRH2, and HRH3 are expressed in the central nervous system as well as other tissues. In contrast, HRH4 is primarily expressed in bone marrow and leukocytes.

The number of neurons in the TMN has been estimated to be as low as 65,000 in primates and 4,000 in rodents. Neurons in the TMN have been tentatively divided into five groups, termed E1-E5. These groups, either collectively or individually, impact sleep, the stress response, and appetite. TMN neuron groups E1 and E2 contribute to wakefulness and food intake whereas the E4 and E5 groups are sensitive to stress and induce secretion of Adrenocorticotropic Hormone, α-Melanocyte Stimulating Hormone, and Prolactin through projections to the paraventricular hypothalamus. The function of the E3 group is not yet known.

KEY:

- 5-Hydroxytryptamine Receptor (5-HTR)
- Adenosine A1 Receptor
- Cannabinoid Receptor 1 (CB1R)
- Dopamine Receptor (DR)
- GABA Receptor (GABA-R)
- Glycine Receptor (GlyR)
- Glutamate Receptor (GluR)
- Growth Hormone Secretagogue Receptor (GHS-R)
- Histamine H3 Receptor (HRH3)
- Kainate Receptor
- M_5 Muscarinic Acetylcholine Receptor
- Metabotropic Glutamate Receptor (mGluR)
- Neurokinin-1 Receptor (NK1R)
- Neurokinin-3 Receptor (NK3R)
- Nicotinic Acetylcholine Receptor (nAChR)
- NMDA Receptor
- κ-Opioid Receptor
- μ-Opioid Receptor
- Opioid Receptor-like 1/Kappa-type 3 Opioid Receptor (ORL1/KOR)
- Orexin Receptor Type 2 (OXR2)
- Potassium Channel, Inward Rectifying (Kir)
- Prostaglandin E Receptor 4 (EP4)
- Purinergic Receptor (P2X and P2Y)
- Sodium Calcium Potassium Exchanger 2 (NCKX2)
- Thyrotropin Releasing Hormone Receptor (TRHR)

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