Chapter 30
Norepinephrine and Synaptic Transmission in the Cerebellum

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Abstract Although the presence of norepinephrine (NE) in the mammalian cerebellum was initially controversial, there is now substantial evidence of a role for the NE system in modulating the response properties of individual cerebellar neurons to synaptic inputs rather than transmitting moment-to-moment details of modality specific information. As a result of these cellular actions the system is capable of regulating cerebellar circuit functions within the context of ongoing voluntary and reflex motor activities and in a manner appropriate to the behavioral state of the organism. The evidence for this mode of operation derives from extensive anatomical, physiological and pharmacological investigations over a period of more than 40 years. This chapter summarizes those studies and the development of this concept.

Keywords Noradrenergic • Locus coeruleus • Neuromodulation • Purkinje cells • Coeruleo-cerebellar pathway

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30.1 Anatomical Considerations

Early fluorescent histochemical (Anden et al. 1967) and biochemical (Iversen and Glowinski 1966) studies provided the first evidence of norepinephrine (NE)-containing fibers within the cerebellar cortex. Later anatomical, physiological, and pharmacological experiments (Bloom et al. 1971; Hoffer et al. 1971a, b; Siggins et al. 1971a, b) confirmed the existence of a prominent NE pathway from the brainstem nucleus locus coeruleus (LC) to all regions of the cerebellar cortex and deep cerebellar nuclei (Olson and Fuxe 1971). Within the cortex, NE fibers arising from LC terminate primarily in the inner portion of the molecular, granule and Purkinje cell layers, with no contact made in the cerebellar white matter (Bloom et al. 1971). The pathway arises exclusively from NE-containing cell bodies in the ipsilateral LC and axons are distributed to virtually every Purkinje cell in every region of the cerebellar cortex. Because of the small number of LC neurons, approximately 1600 per nucleus in rat (Swanson and Hartman 1975), and the broad expanse of cerebellar tissue, it must be assumed that individual LC cells give rise to axons that collateralize extensively throughout the cerebellum.

30.2 Physiology of NE in Cerebellum

NE was initially viewed as an inhibitory transmitter in the cerebellum. However, later studies demonstrated differential effects of NE on spontaneous and evoked discharge of Purkinje neurons that are best described as neuromodulatory (Freedman et al. 1977; Moises et al. 1979; Woodward et al. 1979). NE suppresses Purkinje cell spontaneous discharge but reduces mossy fiber- or climbing fiber evoked excitation to a lesser extent or not all, yielding a net increase in signal to noise ratio, i.e. the ratio of the change in stimulus evoked versus spontaneous discharge. In addition, NE augments inhibitory responses of Purkinje neurons to afferent pathway stimulation (Freedman et al. 1976, 1977). Thus, NE is capable of producing a relative or absolute enhancement of stimulus driven activity in the primary output cells of the cerebellar cortex. Beyond these actions, a ‘gating’ effect has been observed whereby Purkinje cells exhibiting little or no response to peripheral stimuli become responsive to such inputs in the presence of NE (cf Fig. 5 – Moises et al. 1990). Collectively the evidence indicates that NE can produce a spectrum of effects on spontaneous and evoked discharge of Purkinje neurons, all of which serve to regulate the responsiveness of these cells to synaptically-driven inputs.

Further tests showed that NE’s neuromodulatory action on inhibitory transmission was specific for GABA. For example, Moises et al. (1979) showed that glycine-induced inhibition of Purkinje cell firing was not enhanced by NE application and Yeh et al. (1981) showed that NE did not enhance Purkinje cell inhibition elicited by direct application of taurine or beta-alanine, inhibitory amino acids that are structurally similar to GABA. Despite these demonstrations of specificity for GABA, NE can also enhance Purkinje neuron responses to the excitatory amino acid transmitter glutamate (Moises et al. 1979). Importantly, the facilitating effects of NE on amino acid evoked responses in Purkinje neurons have been demonstrated in waking animals (West and Woodward 1984) suggesting these actions are indeed physiologically relevant.

Activation of the noradrenergic input pathway from the LC results in modulatory actions similar to those observed following local application of NE to Purkinje neurons. For example, phasic patterns of LC electrical stimulation that mimic physiologic discharge along the coeruleo-cerebellar pathway result in prominent modulation of Purkinje neuron responses to excitatory and inhibitory synaptic inputs; both climbing fiber and parallel fiber excitation as well as inhibition mediated by local inhibitory interneurons (cf Fig. 5- Moises et al. 1981, cf Fig. 2 – 1983). In addition, LC stimulation increases the probability of Purkinje cell discharge in response to otherwise sub-threshold activation of the climbing fiber input pathway (cf Fig. 5 – Moises et al. 1981). As in other brain regions (Berridge and Waterhouse 2003), these LC-NE modulatory effects follow an inverted-U function (Moises et al. 1981) suggesting that state dependent fluctuations in LC output can adjust cerebellar circuit operations across a dynamic range, one that is capable of optimizing or minimizing function as behavioral contingencies change.

30.3 Noradrenergic Receptors in Cerebellum

The net effect of NE on cerebellar network properties not only depends on the cellular type on which it acts, but also the receptor expression and localization, and concurrent excitatory or inhibitory afferent drive impinging on the neuron. Three main subtypes of adrenergic receptors exist in cerebellum: α_1, β, and α_2, each of which is coupled to a distinct intracellular signaling pathway.

Noradrenergic modulation of inhibitory synaptic activity and GABAergic inhibitory responses in cerebellum are mediated by β-receptor activation (Waterhouse et al. 1982). Binding of NE to this G-protein coupled receptor (GPCR) activates G_s proteins, stimulating intracellular adenylate cyclase, which produces cAMP and activates protein kinase A (PKA). This leads to downstream phosphorylation of an intracellular domain of the GABA receptor, which increases GABA dependent chloride current leading to greater GABA-mediated hyperpolarization of the neuron (Cheun and Yeh 1996; Sweetnam et al. 1988; Kirkness et al. 1989). The modulatory actions associated with activation of cerebellar α_1 and α_2 receptors are less well characterized, but no doubt contribute to NE regulation of cerebellar function.

30.4 Functional Implications

Several reflexes mediated by the cerebellum are modulated by NE, indicating that the effects of NE on individual neuron and neural network properties impact the motor related output of the cerebellum significantly. The vestibular ocular reflex (VOR) stabilizes images on the retina during a head movement by proportionately rotating the eyes in the opposite direction. It has been shown experimentally that β receptor agonists and antagonists are capable of increasing and decreasing, respectively, the ability of this reflex to keep a visual stimulus stabilized on the retina (van Neeven et al. 1990).

In addition to cerebellar reflexes and general motor coordination, motor learning is also heavily influenced by NE in the cerebellum. It has been shown that rats trained to walk across a series of regularly spaced horizontal pegs are able to perform the same task without impairment following 6-OHDA infusion into the brain to destroy NE fibers. The same held true when the pegs were irregularly spaced before and after 6-OHDA infusion. However, when rats were trained initially to walk across the regularly spaced pegs, then received a NE-specific lesion, and later tested on the irregularly spaced pegs, their performance was significantly lower when compared to those performing the same sequence of tasks without the NE-specific lesion (Watson and McElligott 1984). This suggests that the ability of the rats to learn a novel motor task is largely dependent on projections from the LC-NE system to the cerebellum.

30.5 Summary

The cerebellum is prominently innervated by NE fibers arising from the brainstem nucleus LC. The responses of Purkinje neurons in the cerebellar cortex to afferent synaptic inputs are subject to modulation by release of NE from these fibers. Thus, the factors that influence output from the LC also impact the network properties of the cerebellum, e.g. changes in arousal, exposure to stressors. The net outcome of LC-NE regulation of cerebellar circuit operations may be that voluntary and reflex motor activities are optimized with respect to ongoing behaviors and unexpected environmental challenges.

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