Neuropeptides in the Cerebellum

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Abstract

The existence of neuropeptides in the central nervous system has been known for over 50 years with the initial studies being conducted in the early 1970s. At present, a total of 33 neuropeptides have been identified in the cerebellum based on the use of different experimental techniques including immunocytochemistry, in situ hybridization, and gene studies. Indirect evidence for the presence of some neuropeptides has been based on studies that identify the presence of their G-protein coupled receptors. Although 33 cerebellar peptides have been identified, relatively little is conclusively known about the modulatory role of the vast majority of these peptides on cerebellar circuits. Further, the function of peptides produced by cerebellar neurons such as Purkinje cells, Golgi cells, or Lugaro cells is poorly if at all defined. Questions need to be addressed as to the role(s) of neuropeptides in modulating the output of the cerebellum, as carried by the axons of cerebellar nuclear neurons. Future research should focus on determining the mechanism of action of these peptides in modulating neuronal activity including defining transduction pathways activated following the binding of the peptide to its receptor. To truly understand the cerebellar function, it is essential to address the effect of the numerous peptides present within cerebellar circuits and the role they play in modulating neuronal activity in the cerebellum.

Keywords

Neuropeptides · Neuromodulators · G-Protein coupled receptors · Endopeptidase · Exopeptidase · Climbing fibers · Mossy fibers · Purkinje cells · Cerebellar nuclear neurons · Corticotropin-releasing factor · Developmental peptides · Orexin · Dynorphin · Calcitonin gene-related peptide · Spinocerebellar ataxia type 23

36.1 Introduction

The existence of neuropeptides in the central nervous system has been known for over 50 years with the initial studies being conducted in the early 1970s (see Hokfelt for review (Hokfelt 1991). Over the last 50 years, the number of identified neuropeptides in the central nervous system has increased from the initial 15–20 described in the 1970s to nearly 100 today (Ito 2009). Neuropeptides are distinct from cholinergic as well as amino acid and monoaminergic neurotransmitters as described in basic Neuropharmacology textbooks. Nestler and Hyman (2009) provide an excellent overview of neuropeptide synthesis, transport, release, and removal. To summarize their description, neuropeptides are polypeptides that exclusively bind to metabotropic G-protein coupled receptors rather than direct channel ionotropic receptors. Actions mediated by G-protein coupled receptors require activation of second messengers which utilize complex intracellular transduction pathways to alter the response properties of neurons. Thus, because of the steps involved in engaging these signal transduction pathways, there is usually a delay in detecting the onset of the effect of the neuropeptide on its target neuron. Also, the modulatory effect of the peptide is prolonged, compared to that of an amino acid such as glutamate or GABA. When present, the neuropeptides have the potential to alter the responsiveness of neurons to subsequent synaptic inputs. They may become more responsive, if the peptides action is to depolarize the neuron or less responsive if the effect results in hyperpolarization.

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D. L. Gruol et al. (eds.), *Essentials of Cerebellum and Cerebellar Disorders*, https://doi.org/10.1007/978-3-031-15070-8_36

The synthesis of neuropeptides, as for all transmitters, requires transcription of DNA into mRNA and further translation of mRNA into protein (Nestler and Hyman 2009). A unique feature of neuropeptide synthesis is the fact that a single gene may produce several different related neuropeptides in different brain regions. Further, synthesis of peptides occurs only within the cell body of neurons; unlike synthesis of acetylcholine or amino acids which occurs within a nerve terminal. The initial step involves the synthesis of a large pre-propeptide that is further processed into one or more active neuropeptides that are stored in large dense core vesicles in the Golgi apparatus and then actively transported to the axon terminal. These peptide-containing vesicles are present in terminals that also contain amino acid and/or monoaminergic transmitters. Further, more than one peptide may be present within a single terminal.

Within the terminal, large dense core vesicles that contain neuropeptides tend to be located away from the active zone of the terminal, the area immediately adjacent to the postsynaptic target. The mechanism of release is the same as for small vesicles containing amino acids and involves influx of calcium. However, for peptides to be released, more calcium influx is required and it must occur over a longer period so it has time to diffuse to the area of the terminal containing the peptide-filled vesicles. One way to accomplish this enhanced calcium influx would be to have a longer train of action potentials coming down the axon. While a single action potential may result in release of amino acids, a prolonged train may be required to sufficiently depolarize the terminal to allow greater influx of calcium and subsequent release of peptides into the synaptic cleft. Thus peptide release is activity dependent.

Finally, the method for terminating peptide activity is unique from that for amino acids. Their activity is terminated by endopeptidases and exopeptidases located on extracellular membranes of neurons. The concentration of these peptidases is relatively low so neuropeptides may diffuse great distances from the site of their release to remote receptors thus giving them the opportunity to effect larger populations of neurons. These neuropeptides are not transported back into the terminal. All neuropeptides within a terminal must be synthesized within the neuronal cell body and transported to the terminal thus there is the potential for temporary decreases in the availability of peptides for release from axon terminals.

36.2 Neuropeptides in the Cerebellum

Ito (2009) wrote a review that focused on 22 neuropeptides that have been identified in the cerebellum. In his review, Ito (2009) described several different experimental techniques that have been used to identify peptides in the cerebellum including immunocytochemistry to detect the peptide itself and to identify the neuronal element (e.g., axon, soma, axon terminal, glia) in which it is located. A more recent study using a semi-quantitative peptidomic approach (Corbiere et al. 2018) increased the number of peptides in the cerebellum to 33. This study demonstrated that of these 33 peptides, 8 had a clear differential expression pattern during development. Four of these peptides (cerebellin 2, nociception, somatostatin, and VGF [353–372]) exhibited high levels of expression during the first two postnatal weeks followed by a significant decrease in the adult cerebellum. Other studies have used in situ hybridization to detect whether cerebellar neurons express the mRNAs for different peptides. This technique detects peptides produced by cerebellar neurons. Another technique has been to identify genes for specific neuropeptides or their precursors. Again this approach would be limited as finding the gene for a precursor does not establish that the peptide itself is present. Finally, the presence of some neuropeptides is indirectly implied by techniques that identify the presence of their G-protein coupled receptors. Table 36.1 summarizes the distribution of several peptides that have been identified in the cerebellum and their localization in diverse components of cerebellar circuitry including

Table 36.1 Summary of neuropeptide distribution in different neuronal components in the cerebellum determined by immunohistochemistry. Several neurons within the cerebellar cortex express different neuropeptides. Neuropeptides also have been found in afferent systems to the cerebellum including climbing fibers, mossy fibers, and a beaded plexus of axons. Granule cells express receptors for peptides; the origin is yet to be conclusively determined (Adapted from Ito 2009)

Purkinje cell Lugaro cell Golgi cell	Climbing fiber	Mossy fiber	Beaded fiber	Receptors on granule cells
Atrial natriuretic peptide	Corticotropin-releasing factor	Corticotropin-releasing factor	Angiotensin II	A-melanocyte-stimulating hormone
Cerebellin	Insulin-like growth factor 1	Cholecystokinin	Dynorphin	Melanin-concentrating hormone
Motilin	Calcitonin gene-related peptide	Leu-enkephalin	Leu-enkephalin	Neuronal neurotensin
Galanin	Atrial natriuretic peptide	Met-enkephalin	Met-enkephalin	Somatostatin
		Substance P	Orexin	Neuropeptide Y

various cerebellar neurons, the two major afferent systems, climbing fibers and mossy fibers, as well as a beaded plexus of axons. In addition, some granule cells express receptors for specific peptides, although the presence of the neuropeptide itself has not been verified by immunocytochemical techniques. It was suggested that they may be released by mossy fiber terminals although data do not yet support the presence of these peptides in this primary afferent system.

36.3 Role of Peptides in the Cerebellum

It is not possible to discuss the role of all of these peptides in this chapter. It should be noted that the function of most of these peptides in regulating cerebellar circuits remains unclear. One of the major issues with understanding a role for peptides in the cerebellum is due to the fact that their distribution is not uniform within the cerebellum of a particular species and at all ages. Further, it varies between species. However, the action of several peptides has been delineated in some detail. This brief summary will provide an idea of potential roles for some of these peptides in regulating the development and effect on adult cerebellar circuitry.

36.4 Development of the Cerebellum

Cerebellar development is under the control of many different factors. Corbiere et al. (2018) carried out an age-specific analysis to identify peptides at different stages of cerebellar development. They found that four peptides including Cerebellin 2, Nociceptin, Somatostatin, and VGF [353–372] showed high expression at postnatal day (P)8 and were essentially undetectable by P90. In contrast, Cerebellin 1, Octadecaneuropeptide, Secretogranin 1, and WE-14 were upregulated over the same time period. They, and others (Nielsen et al. 1998), further determined that pituitary adenylate cyclase-activated polypeptide (PACAP) was only expressed by Purkinje cells during development. They concluded that peptides expressed only during cerebellar development modulated the survival, migration, and/or differentiation of cerebellar granule cells.

36.5 Adult Cerebellum

The focus will be on four neuropeptides as exemplars for the complex role played by these neuromodulators in the adult cerebellum.

Corticotropin-Releasing Factor: Corticotropin-releasing factor (CRF) is present in climbing fiber and mossy fiber afferent systems in all mammalian species studied to date (Fig. 36.1a and b). CRF in climbing fibers originates from neurons in the inferior olive, whereas CRF in mossy fibers originates from several different brainstem areas including the vestibular complex and the reticular formation (Errico and Barmack 1993; Bishop 1998; Cummings 1989). Neurophysiological studies have shown that CRF is essential in the generation of long-term depression, a mechanism associated with cerebellar learning (Miyata and Ito 1999). Further, CRF has been shown to increase the firing rate of Purkinje cells (Fig. 36.1c and d) by decreasing the amplitude and duration of the after hyperpolarizing potential (Fox and Gruol 1993) and blocking GABA-induced inhibition (Bishop 1990, 1992) (Fig. 36.1e). Clinically, a recent study (Wang et al. 2017) defined a role for CRF released from climbing fibers in the control of gait, posture, and motor coordination which could lead to new strategies for the treatment of cerebellar ataxia. In this study, it was determined that a deficiency of CRF in the olivocerebellar system induces ataxia-like motor abnormalities. Unlike other studies, they determined that this effect was mediated by altering the activity of glutamatergic projection neurons in the cerebellar nuclei leading to deficits in motor coordination.

Orexin: Orexin is present in a beaded plexus of axons that originate from neurons located in the perifornical area and the lateral hypothalamic area of the hypothalamus (Sakurai et al. 1998). These orexinergic axons terminate primarily, if not exclusively within the flocculus of the cerebellum (Nisimaru 2013). Initially, it was hypothesized (Kayaba et al. 2003) that the role of this peptide was to induce a temporary increase in mean arterial blood pressure. More recently, Zhang et al. (2013) suggested that the hypothalamic orexinergic system participates in motor control and integration of somatic (motor) and non-somatic (visceral, emotional, and cognitive) systems. They postulated that a somatic-nonsomatic integration was critical for generation of a coordinated behavioral response to changes in the internal and external environment. The primary effect of orexin was on neurons located in the vestibular nuclei and the cerebellar interpositus nucleus (Yu et al. 2010) which represent a peptidergic effect on the output neurons of the cerebellum and closely related vestibular system. Chen et al. (2013) demonstrated that orexin excited Purkinje cells in the cerebellar cortex as wells as neurons in the cerebellar nuclei. They used eyeblink conditioning to analyze the effects of orexin on this cerebellum-dependent motor learning paradigm. This response has been a standard model system of cerebellar-mediated motor learning. They determined that if they blocked the orexin 1 receptor the timing, rather than the acquisition, of the conditioned eyeblink response was disrupted. This suggested that orexins may modulate motor learning mediated by the cerebellum.

Calcitonin Gene-Related Peptide: Calcitonin Gene-Related Peptide (CGRP) is transiently expressed in climbing

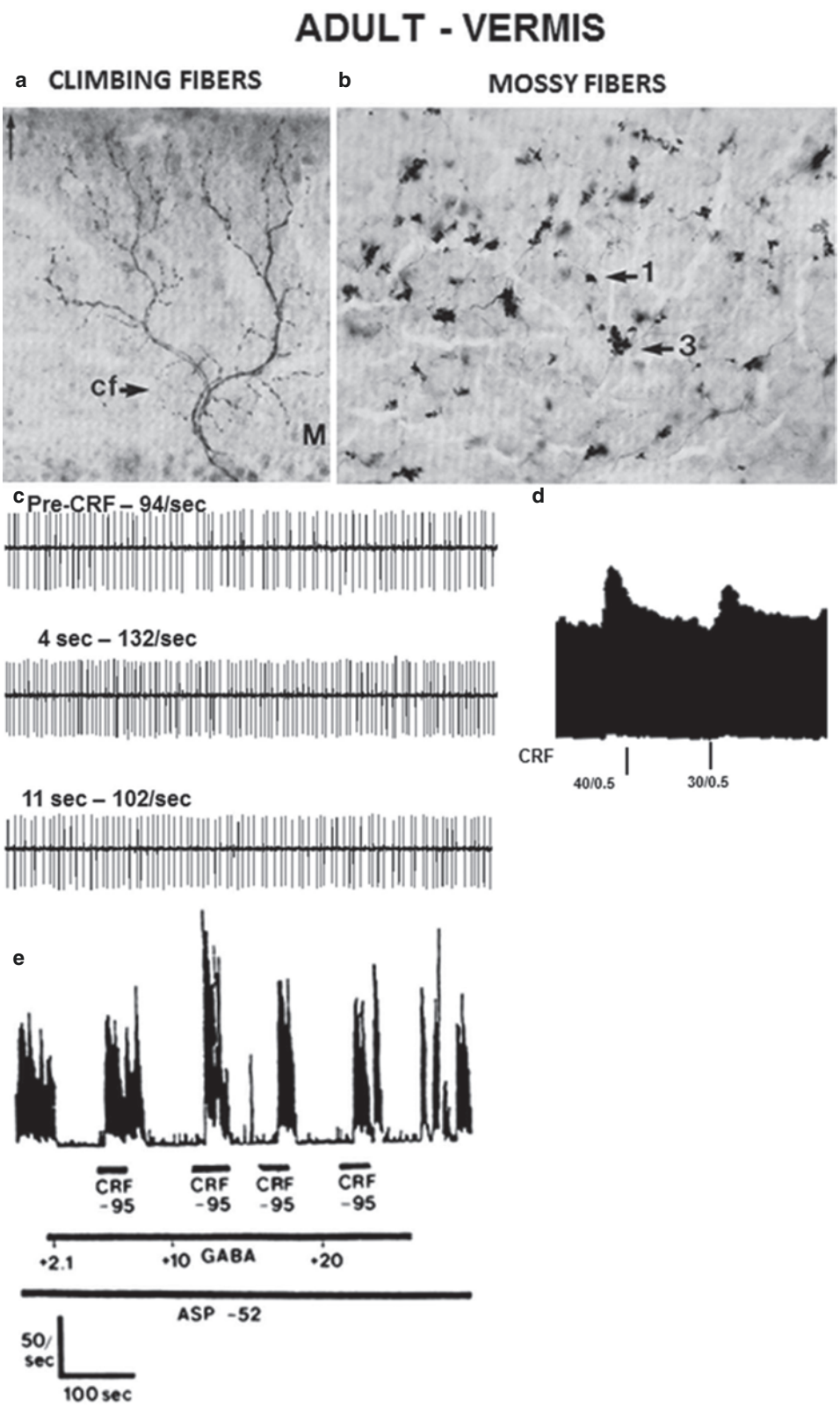

Fig. 36.1 (**a**) CRF-immunolabeled climbing fiber in the opossum cerebellum. (**b**) CRF-immunolabeled mossy fiber in the opossum cerebellum. (**c**) Extracellular recording from a Purkinje cell in the rat's cerebellum. Baseline firing rate was 94 spikes/sec. Four seconds after application of CRF at a pressure of 40 psi for 500 ms, the firing rate increased to 132 spikes/sec. The unit recovered to baseline 11 s after application of CRF. (**d**) Histogram derived from data shown in C. *X*-axis is time. *Y*-axis is spikes/sec. The dashed lines indicate application of CRF at the designated pressure and time. Following application of CRF the firing rate of the Purkinje cell increases and remains elevated for a prolonged period of time. The effect is dose-dependent. (**e**) Histogram documenting interactions between CRF and GABA. This is from a recording in the rat's cerebellum. Application of aspartate causes the neuron to fire at approximately 60 spikes/sec. Application of GABA blocks the aspartate induced excitation, even at low currents. Co-application of CRF during the GABA-induced inhibition blocks the suppressive effect of GABA, even if the inhibitory transmitter is applied at higher doses

fibers during development (Morara et al. 1992). The receptor for CGRP is present on glial cells during early stages of development and on Purkinje cells at later stages (Morara et al. 2008). A calcium imaging study carried out in newborn mice (Morara et al. 2008) concluded that CGRP, released from climbing fibers, modulates calcium in astrocytes during development. During later stages of development, CGRP was shown to stimulate Purkinje cell dendrite growth in culture (D'Antoni et al. 2010) that was dependent on activation of CGRP receptors on astrocytes. A different pattern was observed in the cat's cerebellum, compared to the rat's which demonstrates how peptides have unique distributions and functions in different species. In the cat (Bishop 1992), CGRP was found in mossy fibers in the adult animal. Physiological studies demonstrated that CGRP suppressed spontaneous and excitatory amino acid-induced activity (Bishop 1995). Further, this study demonstrated a synergistic suppressive effect when serotonin and CGRP were administered at the same time. Another point made in this and a previous study (Bishop 1992) was that there was a heterogeneous distribution of CGRP-immunoreactive mossy fibers in the cat's cerebellum suggesting that the effect of this peptide is restricted to specific populations of cerebellar neurons.

Dynorphin: Dynorphin is another peptide localized to a beaded plexus of axons in the cerebellar cortex. Mutations in the prodynorphin gene, the precursor of α-neoendorphin and dynorphins A (Dyn A) and B. Dyn A has been shown to have both opioid and non-opioid activities. Mutations in Dyn A have been associated with the neurodegenerative disorder spinocerebellar ataxia type 23 (SCA23) (Bakalkin et al. 2010; Watanabe et al. 2012; Smeets et al. 2015). SCA23 is characterized by a progressive impairment of motor coordination and the development of classic cerebellar ataxia. This neurodegenerative disorder has been correlated with Purkinje cell death (Verbeek et al. 2004) and loss of climbing fiber innervation (Smeets et al. 2015); these effects are dependent on the presence of NMDA receptors (Tan-No et al. 2001) and appear to involve glutamate neurotoxicity (Bakalkin et al. 2010; Smeets et al. 2015). This, in turn results in loss of Purkinje cells and ataxia seen clinically in a small percentage of SCA23 cases.

36.6 Neuropeptide Receptors

All neuropeptides to date have been shown to bind to G-Protein-Coupled Receptors (GPCRs). Many peptide receptors have been shown to bind more than one peptide of the same family (Nestler and Hyman 2009). For example, the type I CRF receptor preferentially binds CRF but it also has a high affinity for urocortin, a CRF analog. In contrast, the type II CRF receptor binds CRF; however, it has a higher affinity for urocortin. As reviewed in Nestler and Hyman (2009), peptide receptors have a more extensive distribution in the neuropil including extrasynaptic locations (e.g., axons, dendrites outside the area of the synapse). As for the neuropeptides themselves, research on the role of different families of neuropeptide receptors is essential for understanding the role of these ligands in regulating cerebellar activity.

36.7 Conclusion and Future Directions

As is evident from this brief review, there are numerous neuropeptides within the cerebellum. A question might be, why is there a stress hormone (i.e., CRF), or a hypothalamic hormone with a role in sleep (i.e., orexin) or an opioid peptide (i.e., dynorphin) in the cerebellum? That is not the question that should be asked. It is becoming evident that peptides are widely distributed in the central nervous system and that they have unique modulatory functions on different types of neurons. In the cerebellum, some of these peptides, in particular those associated with the climbing fiber and mossy fiber system of afferents (e.g., CRF, orexin and CGRP), have been studied and their physiological effect on Purkinje cells has been reported. These peptides appear to be involved in modulating the excitability of Purkinje cells. In addition, CRF has been shown to be essential for generation of long-term depression in the cerebellar cortex and orexin is postulated to play a role in motor learning as well as integrating inputs from the somatic and autonomic nervous systems in the cerebellum. The opioid dynorphin has primarily been studied in relationship to its role in modulating pain. However, in the cerebellum, mutations in dynorphin have been linked to Spinocerebellar ataxia type 23. This is a unique role for an opioid peptide. The question should not be why are they in the cerebellum, but what is their role in cerebellar control of movement. Functionally, it is important to determine the mechanism by which these peptides modulate neuronal activity. For example, identification of specific second messenger and associated signal transduction pathways is essential. Continued studies on the differential roles for peptides during different stages of development and in the adult also need to be carried out. Further, the role of peptides found within cerebellar neurons such as Purkinje cells, Golgi cells or Lugaro cells is poorly if at all defined. Questions remain as to the effect of these neuropeptides on their postsynaptic targets in the cerebellar cortex and cerebellar nuclei. Another area that requires elucidation is the role of neuropeptides in the cerebellar nuclei. This would include peptides released from the collaterals of climbing and mossy fibers that may release peptides into the nuclei, as well as analysis of peptidergic Purkinje cell axons that terminate in the nuclei. In conclusion, to truly understand cerebellar function, it is essential to incorporate the functional role of the numerous peptides present within cerebellar circuits.

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