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Neuropeptides are selective markers of spinal cord autonomic pathways

The view that various neuropeptides are preferentially present in central autonomic pathways in the mammalian spinal cord is gaining credence. A good example is the vasoactive intestinal polypeptide (VIP)-containing system concentrated in the sacral spinal cord of man and cat, which selectively marks pelvic nerve afferent fibres. Although the functional role of neuropeptides in spinal cord pathways is unknown, their selective appearance provides neurobiologists and pathologists with a new key to understanding the autonomic nervous system.

Classical neuroanatomical tracing techniques have failed to identify clearly the autonomic pathways in the sacral spinal cord. Autonomic neurones are not easily distinguished in conventional histological materials and silver impregnation methods lack sensitivity in demonstrating fine fibres in degeneration studies. Nevertheless, Pick reviewed the classical studies done over the last 100 years and was able to construct a tentative scheme of autonomic connections in the spinal cord. A simplified and composite diagram of the autonomic connections is shown in Fig. 1.

There is an impressive number of different peptide-containing fibres and terminals around cell bodies of the intermediolateral nuclei in thoracic and sacral cord, which form the main autonomic outflow tracts. These include oxytocin in the rat and monkey, vasopressin and oxytocin in man, VIP and peptide histidine isoleucine (PHI) in man and cat, substance P and Met-enkephalin in man and cat, as labelled by retrograde horseradish peroxidase tracing. Dorsal rhizotomy in the cat established, both by immunocytochemistry and quantitatively by radioimmunoassay, that the source of the distinctive VIP-containing system in the sacral cord was the sacral dorsal roots (Fig. 2). De Groat's group combined dye-tracing experiments with histochemistry to demonstrate that VIP and substance P were located in visceral afferent perikarya in the sacral dorsal root ganglia and their terminals in the sacral autonomic nucleus.

The studies of neuropeptides in pelvic nerve afferent fibres illustrate how they may selectively mark autonomic pathways. A VIP-containing system has been discovered in the post-mortem human sacral spinal cord and an investigation of VIP distribution in six mammalian species showed that the monkey and cat sacral spinal cord appeared to be excellent models for that of the human. In man and the other species, PHI-like immunoreactivity co-located with VIP in the sacral cord: it was considered likely, given that VIP and PHI/PHM (peptide histidine methionine) are derived from a common precursor molecule, that they marked the same population of neurones. A striking similarity was observed between the immunocytochemical localization of VIP in human and cat sacral cord and the central termination of fibres from the pelvic nerve of the cat, as labelled by retrograde horseradish peroxidase tracing. Dorsal rhizotomy in the cat established, both by immunocytochemistry and quantitatively by radioimmunoassay, that the source of the distinctive VIP-containing system in the sacral cord was the sacral dorsal roots (Fig. 2). De Groat's group combined dye-tracing experiments with histochemistry to demonstrate that VIP and substance P were located in visceral afferent perikarya in the sacral dorsal root ganglia and their terminals in the sacral autonomic nucleus.

Relapsing and remitting viral diseases of the nervous system

Virus infections can recur intermittently as is painfully appreciated by sufferers of recurrent lesions caused by the herpesvirus. The mechanisms of viral exacerbation and remission have become of interest in the neurosciences with circumstantial evidence that some role is played by viruses in multiple sclerosis. Epidemiological data indicate that multiple sclerosis results from exposure to a virus in childhood followed by a long latency period. The clinical course is typically remitting and relapsing, and the brain and spinal cord contain multifocal demyelinating lesions of different ages. Studies of slow viral infections have now provided many explanations for long incubation periods and studies of both acute and persistent viral infections have shown varied mechanisms of demyelination. Several recent studies of latent and persistent viral infections have provided thought-provoking data on episodic disease.

Recurrent herpetic lesions of the skin are themselves dependent on virus latency in neural cells. This was suspected 80 years ago when surgical section of trigeminal roots to relieve trigeminal neuralgia was found to precipitate herpetic eruptions over the denervated area of the face; but these lesions occurred only when the branches between skin and the corresponding trigeminal ganglia were left intact. Subsequently it has been shown that during oral or genital infections with type 1 or 2 herpes
simplex viruses, the virus moves centrifugally along sensory axons and establishes latency in the neurons of the corresponding sensory ganglia. Productive infection can later be activated by a variety of non-specific stimuli, and virus passes down the nerve to cause the recurrent mucosal or cutaneous vesicles. During latency no virus particles can be seen in the ganglion cells, no antigen can be detected, and virus can be recovered only by organ culture of the ganglia in the laboratory. The virus is presumably latent as viral DNA either integrated into neuronal DNA or sequestered episomally. Selection of the neuron as a host cell for latency is clearly advantageous for the virus, since this static cell provides a lifelong repository for viral genetic information.

A similar pathogenesis has been suspected for varicella-zoster virus to explain the long latency between childhood chickenpox and activation in later life as shingles (herpes zoster), and the dermatomal distribution of the zoster lesions. This more fastidious herpesvirus, however, will not cause similar disease in laboratory animals and has evaded recovery from human ganglia during latency. Two recent studies have demonstrated varicella-zoster virus nucleic acids in trigeminal ganglia of patients without clinical evidence of active infection. Gilden and his co-workers1 hybridized cloned fragments of varicella-zoster DNA virus with normal human trigeminal ganglia and detected sequences of viral DNA at a level of only about one copy per cell. In a complementary study using in situ hybridization, Hyman and colleagues2 detected viral RNA only in neurons and only in about one per 1000 neurons. So the viral genome is there at very low levels, and in rare neurons some RNA appears to be transcribed during latency.

The only RNA viruses capable of similar latency and reactivation are the retroviruses, RNA viruses with a reverse transcriptase that forms a DNA intermediate. These viruses have been associated primarily with tumors, but the subfamily of lentiviruses causes pneumonitis, arthritis and multifocal leukencephalitis in sheep and goats. The leukencephalitis with its long incubation period, relapsing and remitting or progressive course and focal demyelination of differing ages represents the best naturally occurring animal virus model for multiple sclerosis3.

The relapsing clinical course could be explained, in part, by the formation of mutants that are not neutralized by anti-proteins of the parent virus. The localization of lesions might best be explained by latency in oligodendrocytes, but surprisingly the virus appears to be latent primarily in blood monocytes. Recent studies of Narayan and his colleagues4 suggest that migration of these blood monocytes into pulmonary alveoli, joint cavities or the brain is followed by differentiation into macrophages which then provide the right environment for productive infection. The infrequent traffic of macrophage precursors across the blood–brain barrier also might explain the long intervals between attacks and could provide a novel mechanism to explain exacerbations of neurological disease precipitated by trauma or intercurrent infection.

Potential mechanisms for exacerbations of demyelinating lesions have been further extended by studies of a coronavirus, the JHM strain of mouse hepatitis virus. This virus was isolated from a natural paralytic disease of mice and shown to cause an acute demyelinating encephalomyelitis by selective infection of oligodendrocytes. The virus persists in the nervous system of mice and late subclinical inflammatory demyelinating foci do develop. Watanabe and co-workers5 inoculated rats with this murine virus and described a subacute demyelinating encephalomyelitis that developed several weeks to months later, viral antigen was found primarily in glial cells in the neighborhood of the demyelinating plaques. Most rats subsequently recovered despite the persistence of the virus. Lymphocytes from sick rats were cultivated in vitro in the absence of myelin basic protein and then were transferred passively to syngeneic rats. In four or five days mild clinical disease was seen in many recipients and white matter lesions resembling experimental allergic encephalomyelitides were found. Thus, the viral infection of glial cells appears capable of initiating an autoimmune response that could cause exacerbating demyelinating disease.

In the late 1960s and early 1970s two degenerative diseases, kuru and Creutzfeldt-Jakob disease, were transmitted to chimpanzees, and viruses were recovered from two chronic inflammatory diseases, subacute sclerosing panencephalitis and progressive rubella panencephalitis, and a noninflammatory demyelinating disease, progressive multifocal leukencephalopathy. Discovery of a viral etiology for five chronic human neurological diseases in less than a decade raised expectations for recovery of viruses from common neurological disease precipitated by trauma or intercurrent infection.