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Review

Spinal Cord Compression: From Laboratory to Clinic

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INTRODUCTION

THE MAGNITUDE of the clinical problem of neoplastic spinal cord compression (SCC) is usually underestimated. The estimated annual incidence of cancer-induced spinal injury in the U.S.A. is 8.5 per 100 000 [1], which exceeds the calculated incidence of the annual rate of traumatic spinal cord injury (three to five per 100 000). Since SCC in itself is generally not fatal (excluding the upper portion of the cervical spine), treatment is aimed at preserving or restoring ambulation and continence, and alleviating intractable pain. Approximately 50% of the cases of metastatic epidural compression in adults arise from breast, lung or prostatic cancer [2–5], while in children the most common tumour types are different. Sarcomas and neuroblastomas comprise more than 80% of all cases of paediatric SCC [2, 6, 7], and most paediatric tumours invade the spinal canal via the neural foramen rather than via vertebral destruction which is the common mode for neoplastic epidural invasion in adults. These variances usually dictate therapeutic approaches tailored to match the different types of tumour, but the functional outcome still depends on the same pathophysiological mechanism operating in both age groups.

The last two decades have witnessed significant shifts in therapeutic approaches, ranging between urgent decompressive surgery and non-surgical treatments [8]. Regardless of the treatment modality in use, less than 50% of all patients with SCC ever walk again [8], and even prompt decompression does not guarantee neurological recovery. The mechanism that determines the degree of irreversible tissue damage is poorly understood, but appears to be associated with endogenous neurochemical changes resulting from the initial event of compressive injury. Therefore, it seems crucial to link strategies that alleviate compressive mechanical injury with tactics designed to limit the secondary autodestructive processes operating in the compressed spinal cord and leading to neuronal cell death and permanent loss of function.

Comprehension of the neurochemical cascade activated by neoplastic compression has been expanded by the use of newly characterised animal models that enable better understanding of tissue injury at a cellular level [9–21]. The recognition that dynamic biochemical alterations and associated physiological changes occur concomitantly with increasing epidural compression, provided the framework for various experimental treatment approaches. The effectiveness of specific pharmacological strategies also supported hypotheses for roles of proposed injury factors. Laboratory studies demonstrated that pharmacological treatments modify neurochemical changes, attenuate secondary events, such as spinal cord oedema, ameliorate structural neuronal destruction, such as neurofilament disintegration, and significantly delay neurological deterioration, even if the compressing tumour is not removed.

Figure 1 summarises the paradigm of secondary events operating in neoplastic SCC and the pharmacological strategies used to ameliorate them in experimental animal models. The mechanism of injury induced by the expanding extradural tumours is complex and multifactorial. The enlarging extradural tumour causes early obstruction of the spinal epidural venous plexus and enhances production of a vasogenic type of oedema. The oedema involves initially the white matter and in a later stage also the grey matter. At the end, there is a rapid decrease in spinal cord blood flow at the site of compression [10, 11]. Ischaemia may play the final deleterious role, leading to cell death if the compression is not promptly alleviated.

Abnormalities in spinal somatosensory evoked responses precede neurological signs of myelopathy in an animal model of SCC [13]. The conduction block may be related to myelin destruction demonstrated by an electron microscopy study [13]. The disruption of myelin is probably caused by mechanical compression, by local toxic effects of cytokines mediating the inflammatory response and by ischaemia. Although it is now clear that demyelination can occur at sites of SCC [22, 23], remyelination may take place after transient compression [24], providing a possible morphological correlate for recovery of function following prompt decompression.

Local production of cytokines, such as prostaglandins, interleukin (IL)-1 and IL-6, may promote an inflammatory response with its associated physiological changes of vasodilatation, plasma exudation and oedema formation [25, 26]. In fact, elevation of PGE_2 synthesis has been consistently demonstrated in the compressed cord concomitantly with the development of spinal cord oedema [15–17]. In keeping with that concept, an antioedema effect is achieved when partial or marked reduction of PGE_2 synthesis is accomplished either by steroidal, or non-

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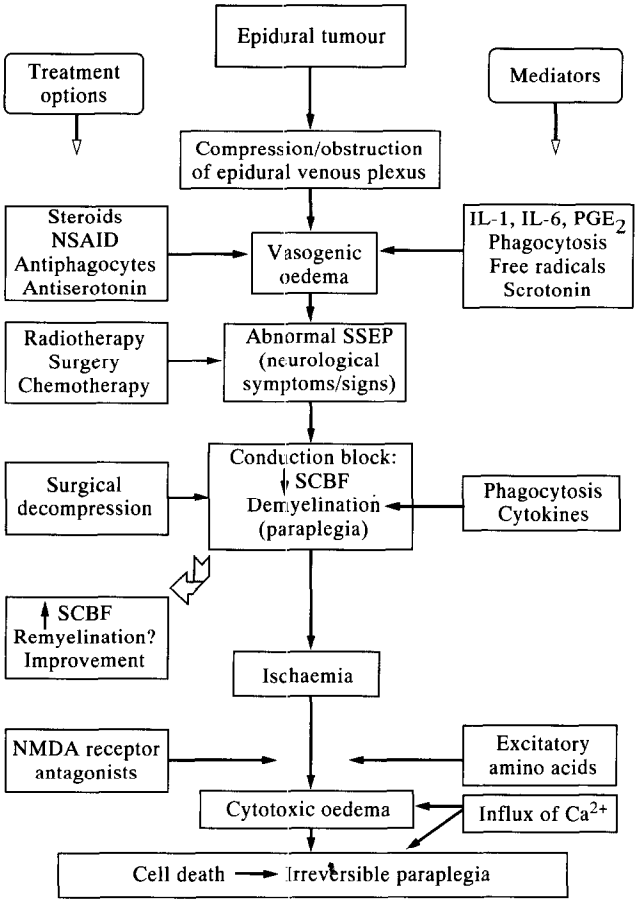

Figure 1. An algorithm of the recognised mechanisms involved in the pathophysiology of neoplastic SCC. Treatment options represent possible pharmacological intervention that may reduce neural tissue damage. Most of the data related to pharmacological manipulations are derived from investigation of animal models of neoplastic SCC. The relationship of the currently used therapeutic modalities in humans (corticosteroids, radiotherapy, surgery and chemotherapy) to the specific stage of spinal cord injury is also demonstrated. SCBF, spinal cord blood flow; NMDA, *N*-methyl-D-aspartate; SSEP, spinal somatosensory-evoked potential.

steroidal anti-inflammatory drugs (e.g. indomethacin) [16, 17] or by inhibitors of phagocytic activity [25, 26].

PHAGOCYTOSIS, TISSUE INJURY AND VASOGENIC OEDEMA

Local production of substances such as cytokines may amplify the cascade ending in demyelination and tissue injury. The central nervous system contains a cytokine network that is important for normal function, and thus cytokine production is one of the characteristics shared by microglia and astrocytes [27, 28]. An increase in the production or release of cytokines can convert a normal action into a toxic property [29]. Cytokines, such as IL-1 and tumour necrosis factor, have been identified as mediators in a variety of demyelinating processes when released by activated macrophages together with other cytokines [30]. Microglia are the representatives of the mononuclear phagocytic system in the central nervous system (CNS) [31], and may participate in tissue destruction either directly or indirectly through the release of toxic substances, such as free radicals and cytokines. The engagement of spinal cord phagocytes in clearing myelin debris was demonstrated by an electron microscopy study in experimental neoplastic SCC [13]. Evidently, this process of phagocytosis induces a release of soluble mediators of inflammation into the extracellular space of the compressed cord segments [23].

The possible role of microglia in neoplastic SCC was further investigated in a recent study that used immunohistochemistry techniques and pharmacological inhibition of phagocytosis and cell migration [22, 23]. In tumour-bearing paraplegic rats, immunohistochemistry studies showed that the normal population of resting microglial cells was replaced by activated amoeboid cells, probably engaged in phagocytosis (Figure 2). In addition, at onset of paraplegia, marked disruption of normal neurofilament cytoarchitecture was evident (Figure 3).

In vivo inhibition of phagocytosis, achieved by pharmacological interference, blocked lysosomal activity and cell migration by combined treatment with chloroquine and colchicine. Treatment was initiated at the onset of neurological dysfunction and continued until paraplegia developed. In treated rats, the ratio of amoeboid microglia (activated phagocytes) was clearly reduced. In addition, marked preservation of neurofilament structure was evident at the onset of paraplegia, unlike the massive destruction observed in untreated animals (Figure 3). This treatment also reduced the enhanced synthesis of cytokines (PGE_2, IL-1 and IL-6) which were elevated in untreated, paralysed rats. The 10-fold increase in microvascular permeability present in untreated paralysed rats was attenuated by 60% as a result of the inhibition of phagocytic activity, further indicating that the inflammatory response actively propagated oedema formation. Initiation of treatment at the first signs of neurological dysfunction significantly delayed the onset of paraplegia and protracted the course of neurological deterioration toward paraplegia by 77% (Figure 4). These results suggest that in SCC, phagocytic activity with its related by-products (cytokines), probably participates in the mechanism of cord injury. Inhibition of phagocytosis may delay structural damage and thus enhance chances for recovery following prompt decompression by antitumour therapy.

VASOGENIC OEDEMA AND SEROTONERGIC MECHANISMS

The possibility that serotonergic mechanisms participate in the autodestructive events operating in neoplastic SCC was recently investigated. The hypothesis was that the monoaminergic neurotransmitter serotonin (5-HT) which plays an important role in some inflammatory responses (such as neurogenic inflammation) may have a role in propagating spinal cord damage. Indeed, we demonstrated that a marked increase in the utilisation of 5-HT was present in the compressed cord segments [20, 21]. However, it was still unclear whether the increased utilisation of 5-HT was linked to disruption of the blood–spinal cord barrier and whether activation of 5-HT receptors induced an increase in the synthesis of PGE_2. By pharmacological manipulation with *p*-chlorophenylalanine, we were able to demonstrate that *in vivo* depletion of the 5-HT level significantly attenuated the increased vascular permeability of the compressed spinal cord and also delayed deterioration of neurological function (Figure 4). A selective *in vivo* blockage of 5-HT type 2 ($5\text{-}HT_2$) receptors, located mostly on neuronal and vascular tissues, was achieved by treatment with ketanserin. This selective inhibitor produced a dose-related effect, with similar attenuation in spinal cord vascular permeability and with a protraction of the course of the disease towards paraplegia (Figure 4). Yet, it has become clear that $5\text{-}HT_2$ receptor activation plays only a minor role in PGE_2 production in the compressed cord, since all

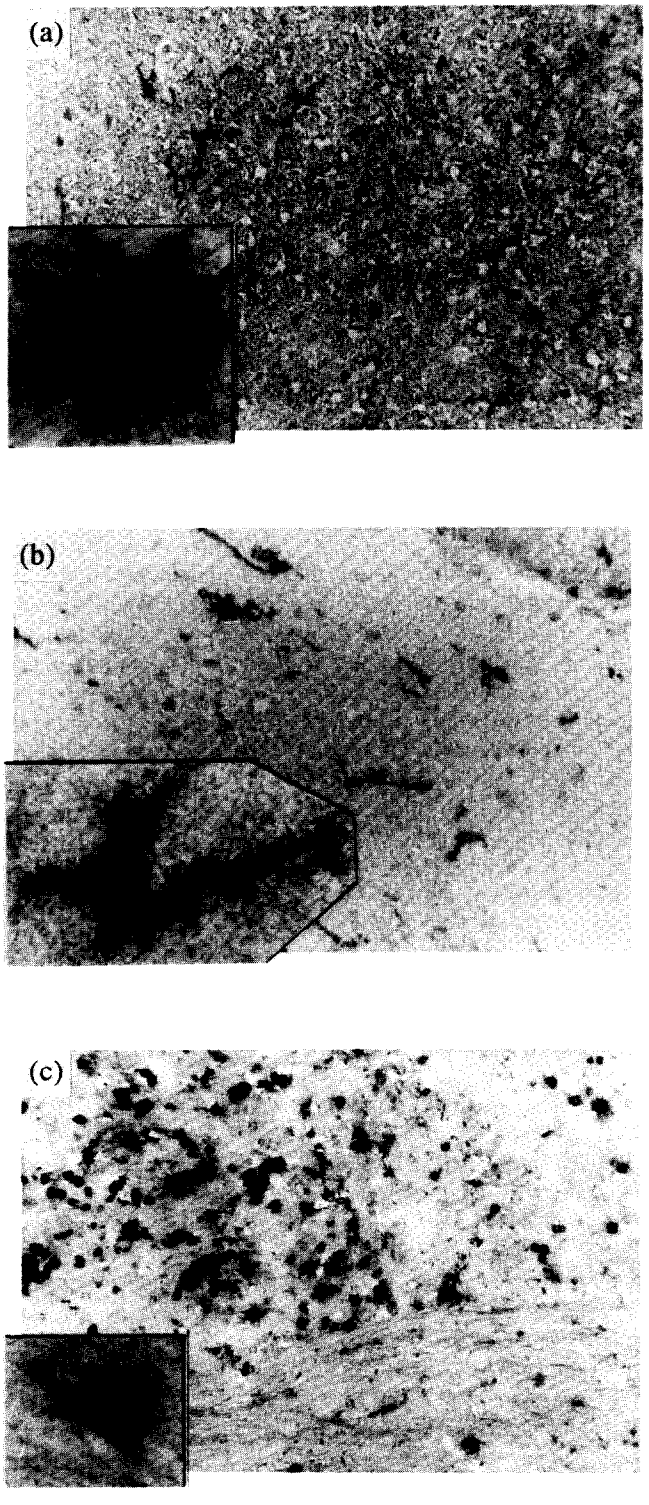

Figure 2. An immunohistochemistry staining of the spinal cord with OX42—a specific microglial marker. (a) The normal pattern of non-activated resident microglia in the spinal cord (×164). The typical configuration of a ramified cell is demonstrated in large magnification in the insert (×1640). (b) The microglial pattern found at the time of onset of first signs of neurological dysfunction (while the rats can still walk and climb) (×164). The cells are activated and undergoing transition into phagocytes. Transitional cells are identified by their condensed, shortened and thick processes better seen with higher magnification in the insert (×1640). (c) An increased number of amoeboid (phagocytic) cells identified in the compressed spinal cord segment on the day of onset of paraplegia (×164). The cells are round with only a few or no processes as demonstrated with higher magnification in the insert (×1640).

the specific serotonergic manipulations failed to reduce PGE_2 synthesis [21]. In contrast, the same *in vivo* pharmacological inhibition of 5-HT_2 receptors, when applied to normal animals, produced significant attenuation of spinal cord PGE_2 synthesis. These results suggest that 5-HT is an important generator of prostaglandin synthesis in the normal spinal cord, but in the pathological state, other more vigorous constituents trigger the abnormal production of PGE_2. It has also become clear that the mechanism by which 5-HT alters the blood–spinal cord barrier permeability is distinct from the mechanism associated with the inflammatory response. Each one of these two mechanisms can be *separately* manipulated pharmacologically to yield measurable, favourable effects in the experimental model. It is still unclear whether a combined pharmacological regimen will result in an additive effect.

ISCHAEMIC–HYPOXIC NEURONAL INJURY AND CYTOTOXIC OEDEMA

When conduction block and ischaemia are present in the final stages, neuronal injury and cytotoxic oedema will develop. The cytotoxic oedema, unlike the vasogenic oedema, results from failure of the energy-dependent membrane ionic pumps, and this leads to intracellular accumulation of sodium and chloride, swelling of the cells and a delayed cell death. Over the past few years, attention has been drawn to the possibility that the glutamate system may play a central role in the pathogenesis of hypoxic–ischaemic neuronal injury [32].

Glutamate and related amino acids are excitatory neurotransmitters that are essential for central neuronal processing. Large amounts of glutamate are present in the brain and spinal cord, normally stored in presynaptic terminals and other intracellular locations. During CNS ischaemia, a rapid increase in extracellular glutamate takes place. Its accumulation is secondary to an increased synaptic release occurring in the face of an impaired cellular uptake. Excessive exposure to extracellular glutamate can destroy central neurons.

The mechanisms underlying glutamate neurotoxicity are not fully defined, but results of *in vitro* experiments have suggested two components: acute excitotoxic neuronal swelling, secondary to the influx of chlorine and sodium, and delayed neuronal disintegration due to the influx of calcium [32, 33]. While calcium probably enters via several routes, including voltage-gated channels, membrane channels are opened by activation of the *N*-methyl-D-aspartate (NMDA) receptor subtype, which is most important for glutamate-mediated injury. Sustained elevation of cytosolic calcium is likely to produce lethal disturbances in the many biological processes regulated by calcium availability, including especially the activation of intracellular proteases and lipases and the generation of free radicals. In addition, calcium entry into neuronal presynaptic terminals could increase the release of endogenous glutamate, further propagating injury via a positive feedback mechanism.

Glutamate activates other receptors in addition to NMDA receptors, but only the latter are linked to membrane channels with high permeability to calcium. Thus, selective NMDA antagonists only partially reduce glutamate-induced neuronal excitation, but almost completely abolish glutamate-induced late neuronal loss [34, 35]. Competitive NMDA antagonists directly block the glutamate recognition site [36], but they are relatively polar and, therefore, their *in vivo* efficacy is limited by the blood–brain barrier. Available non-competitive NMDA antagonists do not compete for binding at glutamate recognition sites, but associate with the phencyclidine site within the NMDA

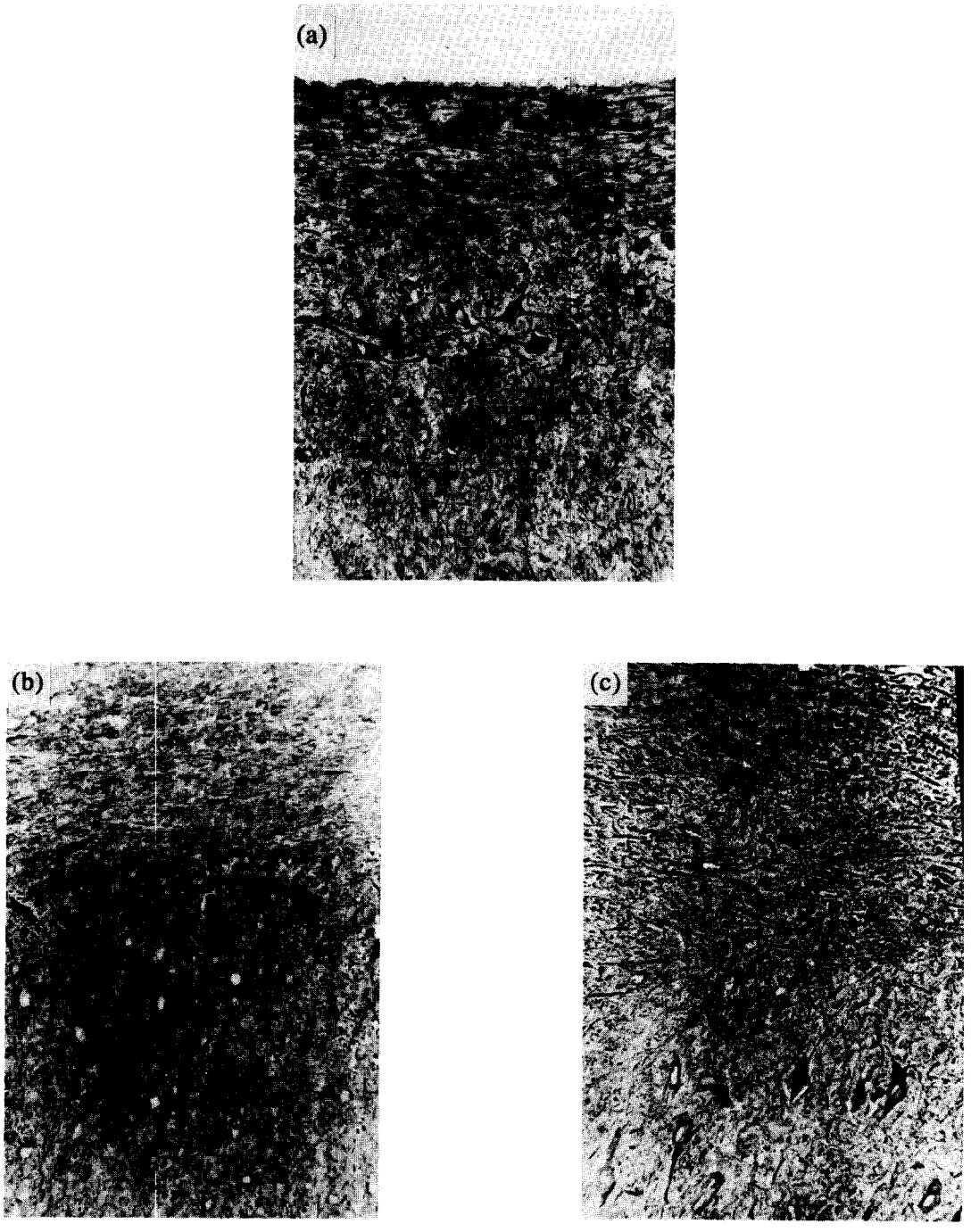

Figure 3. Immunohistochemistry staining for 200 kDa neurofilaments (phosphorylated and non-phosphorylated neurofilaments). (a) The normal pattern of neurofilament cytoarchitecture in the white (W) and grey (G) matter of the spinal cord (×164). (b) On the day of onset of paraplegia, there is marked disruption of the normal neurofilament cytoarchitecture evident in both the white and grey matter of the spinal cord. The damage is more severe in the white matter. (c) Marked preservation of neurofilament cytoarchitecture obtained on the day of onset of paraplegia in animals treated with antiphagocytic drugs. The antiphagocytic treatment with chloroquine and colchicine blocked lysosomal acitivity and cell migration, while the epidural tumour continued to enlarge until it eventually induced paraplegia. Treatment was initiated at onset of neurological dysfunction and continued until paraplegia developed.

receptor-activated membrane channel, thereby impeding ionic current through the channel [37]. These compounds, which readily cross the blood–brain barrier, include the dissociative anaesthetic, ketamine, and the dibenzocycloheptenimine, MK-801. The use of this subclass of glutamate receptor antagonists has yielded encouraging results in a variety of experimental models of hypoxic–ischaemic neuronal injury [32].

In neoplastic SCC, ischaemia occurs late in the process of epidural compression, when spinal cord blood flow decreases rapidly at the site of pressure, resulting in ischaemic injury and paraplegia [10, 11]. At this stage, glutamate neurotoxicity may account for neuronal death and irreversibility of the neurological deficit. The use of glutamate receptor antagonists may offer some protection against excitotoxic neuronal injury, pending restitution of normal regional perfusion by immediate decompressive surgery and alleviation of local pressure. Experimental studies have demonstrated that, in neoplastic SCC, cytotoxic oedema is probably present and excitotoxins (like glutamate) are

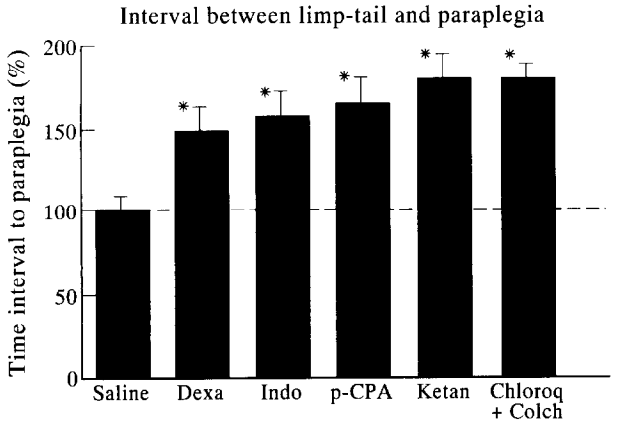

Figure 4. The effect of early pharmacological intervention on neurological deterioration in experimental animal models of neoplastic spinal cord compression. The bar graph summarises the results of the experimental studies in rats in which the effect of treatment on the clinical course of the disease was measured as the interval between the first sign of neurological dysfunction (hypotonic tail = limp tail) and the onset of paraplegia. Treatment with either anti-inflammatory or with antiserotonergic agents was started on the day the first neurological sign was observed in the experimental animals and continued daily until paraplegia developed. Saline is treatment given to control animals harbouring an epidural tumour. Dexa, dexamethasone; Indo, indomethacin; p-CPA, *p*-chlorophenylalanine (induces *in vivo* depletion of serotonin level); Ketan, ketanserin (a specific serotonin type 2 receptor antagonist); Chloroq + Colch, chloroquine plus colchicine (inhibit, respectively, lysosomal and cell migration activity, antiphagocytic). *Statistical significant difference, $P<0.02$.

likely mediators in its evolution [18, 19]. In these studies, the non-competitive glutamate receptor antagonists, ketamine or MK-801, produced an anti-oedema effect in the compressed spinal cord. This anti-oedema effect was *uncoupled* from inhibition of PGE_2 synthesis and had no effect on the increased vascular permeability, which is the hallmark of vasogenic oedema. It suggests that cytotoxic oedema is present in the compressed spinal cord and that pharmacological intervention may partially prevent its evolution. Early administration of these glutamate receptor antagonists had no effect on the course of neurological deterioration toward paraplegia, implying that excitotoxic injury is a late event in neoplastic compression damage.

LESSONS LEARNED: IMPLICATIONS FOR THERAPY

Summarising the current knowledge derived from experimental animal models, it becomes clear that the mechanism of tissue damage evidently arises from increasing mechanical pressure that then triggers a dynamic process, which is just beginning to be understood. The response to the mechanical compression involves both an early inflammatory cytotoxic injury and hypoxic–ischaemic damage in the advanced staged. Neurotransmitters, such as serotonin and glutamate, actively participate in the cascade, leading to an irreversible neurological deficit. Accordingly, early pharmacological intervention may constitute an effective means of interrupting tissue destruction and degeneration, thereby preserving normal cellular architecture, permitting neurological recovery. Figure 4 summarises the experimental findings which indicate that early pharmacological intervention may potentially delay neurological deterioration. However, it is still unclear whether the use of glutamate receptor antagonists may offer any clinical benefit.

An important and still uninvestigated issue is the potential benefit of combined pharmacological regimens, aiming concomitantly at different receptor sites and at uncoupled pathophysiological mechanisms (e.g. using together antiserotonergic, anti-inflammatory and NMDA receptor antagonists). Whether an additive beneficial effect can be obtained awaits further experimentation. Such studies may provide a basis for novel therapeutic approaches. However, because of the complexity of the enumerated pathophysiological mechanisms, pharmacological manipulations should first be carefully assessed in animal models. It should be determined which agents are most efficacious, what is the optimal dose and time of administration of a single agent, and how they should be modified when a combined pharmacological attack is utilised. All should be assessed in terms of clinical benefit prior to the extrapolation of early laboratory results into human clinical studies.

1. Murray PK. Functional outcome and survival in spinal cord injury secondary to neoplasia. *Cancer* 1985, **55**, 197–201.
2. Byrne NT. Spinal cord compression from epidural metastases. *N Engl J Med* 1992, **327**, 614–619.
3. Bach F, Larsen BH, Rohde K, *et al.* Metastatic spinal cord compression. Occurrence, symptoms, clinical presentations and prognosis in 398 patients with spinal cord compression. *Acta Neurochir* 1990, **107**, 37–43.
4. Constans JP, De Divitiis E, Donzelli R, Spaziante R, Meder JF, Haye C. Spinal metastases with neurological manifestations: review of 600 cases. *J Neurosurg* 1983, **59**, 111–118.
5. Landmann C, Hunig R, Gratzi O. The role of laminectomy in the combined treatment of metastatic spinal cord compression. *Int J Radiat Biol Phys* 1992, **24**, 627–631.
6. Raffel C, Neave VCD, Lavine S, McComb JG. Treatment of spinal cord compression by epidural malignancy in children. *Neurosurgery* 1991, **28**, 349–352.
7. Klein SL, Sanford RA, Muhlbauer MS. Pediatric spinal epidural metastases. *J Neurosurg* 1991, **74**, 70–75.
8. Siegal T, Siegal Tz. Epidural spinal metastases from solid tumors. In Keyser A, Ongerboer de Visser BW, Twijnstra A, eds. *Neuro-Oncology*. Amsterdam, Elsevier Science Publishers B.V., 1993, 283–305.
9. Ushio Y, Posner R, Posner JB, Shapiro WR. Experimental spinal cord compression by epidural neoplasms. *Neurology* 1977, **27**, 422–429.
10. Ikeda H, Ushio Y, Hayakawa T, *et al.* Edema and circulatory disturbance in the spinal cord compressed by epidural neoplasms. *J Neurosurg* 1980, **52**, 203–209.
11. Kato M, Ushio Y, Hayakawa T, Yamada K, Ikeda H, Mogami H. Circulatory disturbance of the spinal cord with epidural neoplasm in rats. *J Neurosurg* 1985, **63**, 260–265.
12. Delattre JY, Arbit E, Thaler HT, Rosenblum MK, Posner JB. A dose–response study of dexamethasone in a model of spinal cord compression caused by epidural tumor. *J Neurosurg* 1989, **70**, 920–925.
13. Siegal T, Siegal Tz, Sandbank U, *et al.* Experimental spinal cord compression: evoked potentials, edema, prostaglandins, light and electron microscopy. *Spine* 1987, **12**, 440–448.
14. Siegal T, Siegal Tz, Shapira Y, Sandbank U, Catane R. Indomethacin and dexamethasone in experimental neoplastic spinal cord compression: Part I. Effect on water content and specific gravity. *Neurosurgery* 1988, **22**, 328–333.
15. Siegal T, Shohami E, Shapira Y, Siegal Tz. Indomethacin and dexamethasone in experimental neoplastic spinal cord compression: Part II. Effect on edema and prostaglandin synthesis. *Neurosurgery* 1988, **22**, 334–339.
16. Siegal T, Siegal Tz, Shohami E, Shapira Y. Comparison of soluble dexamethasone sodium phosphate with free dexamethasone and indomethacin in the treatment of experimental neoplastic spinal cord compression. *Spine* 1988, **13**, 1171–1176.
17. Siegal T, Siegal Tz, Shapira Y, Shohami E. The early effect of steroidal and non-steroidal anti-inflammatory agents on neoplastic epidural cord compression. *Ann NY Acad Sci* 1989, **559**, 488–490.
18. Siegal T, Siegal Tz, Shohami E, Lossos F. Experimental neoplastic

spinal cord compression: effect of ketamine and MK-801 on edema and prostaglandins. *Neurosurgery* 1990, **26**, 963–966.
19. Siegal T, Siegal Tz. Experimental neoplastic spinal cord compression: effect of anti-inflammatory agents and glutamate receptor antagonists on vascular permeability. *Neurosurgery* 1990, **26**, 967–970.
20. Siegal T, Siegal Tz. Participation of serotonergic mechanisms in the pathophysiology of experimental neoplastic spinal cord compression. *Neurology* 1991, **41**, 574–580.
21. Siegal T, Siegal Tz. Serotonergic manipulations in experimental neoplastic spinal cord compression. *J Neurosurg* 1993, **78**, 929–937.
22. Blight A. Morphometric analysis of experimental spinal cord injury in the cat: relationship of injury intensity to survival of myelinated axons. *Neuroscience* 1986, **19**, 321–341.
23. Waxman SG. Demyelination in spinal cord injury. *J Neurol Sci* 1989, **91**, 1–14.
24. Gledhill RF, McDonald WI. Morphological characteristics of central demyelination and remyelination: a single-fibre study. *Ann Neurol* 1977, **1**, 552–560.
25. Siegal T, Shezen E, Siegal Tz. The effect of *in vivo* inhibition of phagocytic activity in experimental neoplastic spinal cord compression: immunohistochemistry, vascular permeability and neurologic function. *J Neuro-Oncol* 1994, **21**, 68.
26. Siegal T, Shezen E, Barak V, Siegal Tz. *In vivo* inhibition of phagocytic activity in experimental neoplastic spinal cord compression: immunohistochemistry, cytokines production, vascular permeability and neurologic function. *Neurology* 1995, **45**, 193A.
27. Dickson DW, Lee SC, Mattiale LA, Yen SH, Brosnan C. Microglia and cytokines in neurological disease, with special reference to AIDS and Alzheimer's diesase. *Glia* 1993, **7**, 75–83.
28. Sawada M, Kondo N, Suzumura A, Marunouchi T. Production of tumor necrosis factor-alpha by microglia and astrocytes in culture. *Brain Res* 1989, **491**, 394–397.
29. Balkwill FR, Burke F. The cytokine network. *Immunol Today* 1989, **10**, 299–304.
30. Hartung H-P. Immune-mediated demyelination. *Ann Neurol* 1993, **33**, 563–567.
31. Hickey WF, Krimura H. Perivascular microglial cells of the CNS are bone-marrow derived and present antigen *in vivo*. *Science* 1988, **239**, 290–292.
32. Albers GW, Goldberg MP, Choi DW. *N*-Methyl-D-aspartate antagonists: ready for clinical trials in brain ischemia? *Ann Neurol* 1989, **25**, 398–403.
33. Choi DW. Ionic dependence of glutamate neurotoxicity in cortical cell culture. *J Neurosci* 1987, **7**, 369–379.
34. Choi DW, Koh J, Peters S. Pharmacology of glutamate neurotoxicity in cortical cell culture: attenuation by NMDA antagonists. *J Neurosci* 1988, **8**, 185–196.
35. Stewart GR, Olney JW, Pathikonda M, Snider WD. Excitotoxicity in the embryonic chick spinal cord. *Ann Neurol* 1991, **30**, 758–766.
36. Watkins JC, Olverman HJ. Agonists and antagonists for excitatory amino acid receptors. *Trends Neurosci* 1987, **10**, 265–272.
37. Kemps JA, Foster AC, Wong EHF. Non-competitive antagonists of excitatory amino acid receptors. *Trends Neurosci* 1987, **10**, 294–298.