ANIMAL MODELS OF SPINAL CORD INJURY PAIN AND THEIR IMPLICATIONS FOR PHARMACOLOGICAL TREATMENTS

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Patients with spinal cord injury often develop chronic pain syndrome, which is difficult to treat. Several animal models of spinal cord injury have been developed in recent years which have significantly advanced our understandings of pathophysiology of this condition. This paper reviews some recent data in the pharmacological treatment of spinal cord injury pain using animal models, and discusses possible clinical applications.

Key words: allodynia, analgesia, central pain, spinal cord injury pain

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INTRODUCTION

A substantial portion of patients with spinal cord injury (SCI) suffer chronic debilitating pain (1). SCI pain is mostly of mixed types, although that of a neuropathic pain nature appears to be most troublesome for clinical pain management (2). Neuropathic pain following SCI resembles in many aspects the clinical characteristics of neuropathic pain of other origins. It can be either spontaneous pain, often intensified by physical activity and exposure to cold, paroxysmal pain or evoked pain. The latest classification suggests that SCI pain of the neuropathic type can be divided into three subtypes: below, at and above the level of injury (2). Neuropathic SCI pain is difficult to treat and no treatment algorithm has ever been established. Moreover, mechanisms underlying SCI pain remain obscure, which has further contributed to the lack of progress in finding effective treatments.

ANIMAL MODELS OF SPINAL CORD INJURY PAIN

Recent years have seen major advances in the development of animal models of SCI pain, which has significantly advanced our understanding of the pathophysiology of this condition. These models are being used to explore effective pharmacological treatments (3–5).

In our laboratory, we used a photochemical technique to generate ischaemic SCI. In addition to motor deficits and morphological damage, which were expected sequelae of spinal cord damage, we observed behavioural signs suggesting the presence of tonic (days) and chronic (months) pain-related sensations in spinally injured rats (6, 7). The chronic allodynia-like behaviour only developed in a subgroup of rats after severe ischemia and with extensive spinal cord lesions. The main symptom of this chronic pain-related syndrome is marked segmental mechanical and cold allodynia (7). We also observed autotomy of the hind paws and excessive scratching behaviour in some allodynic animals, which may indicate the presence of ongoing pain and/or dysesthesia (7). We have performed extensive studies in characterising this chronic pain-related syndrome and the results revealed remarkable similarities between our model and symptoms observed in patients with chronic pain after SCI. We have therefore suggested that the chronic allodynia-like symptoms observed in rats after spinal cord ischemia can be regarded as an animal model of SCI pain of the at-level type (2, 4).

PHARMACOLOGY OF THE CHRONIC ALLODYNIA-LIKE BEHAVIOURS

Opioids

In agreement with the clinical impression that opioid analgesics are not effective in SCI pain, we found that systemic morphine only alleviated chronic allodynia at doses which produced severe sedation (7, 8). In contrast, direct spinal administration of intrathecal (i.t.) morphine was effective (8). The potency of the anti-allodynic effect of i.t. morphine was however reduced compared to its antinociceptive effect, and there was a rapid development of tolerance to the effects of i.t. morphine in spinally injured rats (8, 9). Thus, morphine is clearly less potent in alleviating central pain-like behaviours in spinally injured rats. Although spinal administration of morphine is effective initially, it is unclear whether mono-therapy with i.t. morphine could provide long-term relief in patients with SCI pain, as tolerance development may present a problem.

In addition to morphine which acts primarily on the mu-opioid receptor, selective opioid receptor agonists acting on the delta, but not kappa, receptor produced anti-allodynic effect in this model upon i.t. administration (10). The same is also true for nociceptin which is the endogenous ligand for the 4th member of the opioid

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receptor family, OP4 (11). Drugs of these types may thus be useful in treating SCI pain.

Alpha2-adrenoceptor agonists

Several clinical studies have shown that spinal administration of the ⁄ 2-adrenoceptor agonist clonidine relieves neuropathic SCI pain (12, 13). Similarly, we observed that i.t. clonidine dose-dependently alleviated chronic allodynia-like behaviour in spinally injured rats without producing major side effects such as sedation or a drop in blood pressure (14). In contrast, systemic clonidine was without effect at sub-sedative doses (14). Interestingly, in one clinical study, whereas clonidine per se produced a small and non-significant effect, the combination of morphine and clonidine relieved SCI pain in about 50% of patients, indicating a synergistic effect (15). This agrees with an extensive literature in basic research demonstrating synergistic interaction in producing antinociception between opioids and ⁄ 2-adrenoceptor agonists (16), suggesting that combination treatment may be useful in neuropathic SCI pain.

Adenosine

Adenosine is an endogenous purine nucleotide which is extensively distributed intra- and extracellularly in the nervous system (17). Activation of spinal adenosine A1 receptors has been shown to produce antinociception (18). In a recent series of studies we have shown that i.t. R-phenylisopropyladenosine (R-PIA), an adenosine A1 receptor agonist, effectively alleviated chronic allodynia in spinally injured rats (19, 20). The antiallodynic effect of R-PIA persisted considerably longer than that of morphine upon repetitive administration (20) and there was a synergistic interaction between R-PIA and morphine (21). Finally, no cross-tolerance was seen between the anti-allodynic effect of i.t. R-PIA and morphine (20).

Anti-epileptic drugs

Anti-epileptic drugs are commonly used in neuropathic pain. In one earlier clinical study, valproate was found to be not significantly better than placebo in treating SCI pain (22). However, several recent pilot studies have identified the efficacy of newer epileptic drugs such as gabapentin and topiramate (23–25). This was supported by experimental studies by us and others, at least for gabapentin. Thus, we observed that repeated systemic gabapentin alleviated chronic pain-like behaviours in spinally injured rats with no side effects (26). Hulsebosch et al. (27) also found that systemic gabapentin alleviated mechanical and heat hypersensitivity in rats after spinal hemisection and normalised the activity level in the sleep cycle in spinally injured rats.

Sodium channel blockers

Sodium channels play a key role in neuronal hyperexcitability and may thus be important in generating SCI neuropathic pain. Sodium channel blockers such as lidocaine or mexiletine are frequently used in neuropathic pain, and in two published trials, spinal or intravenous lidocaine was found to be effective in SCI neuropathic pain (28, 29). In our experience with the rat model, the lidocaine derivative tocainide and mexiletine are effective and consistent in producing anti-allodynia (7, 30, 31). The problem is that they tend to have a small therapeutic window between effective and toxic doses, which may limit their clinical application. This may be reflected in the poor tolerability for mexiletine in the clinic.

N-methyl-D-aspartic acid (NMDA) receptors antagonists and nitric oxide inhibitors

NMDA receptor activation is essential for pain processing, pain sensitisation and neuronal plasticity (32). Production of nitric oxide is one of the important mechanisms by which NMDA receptor exerts its physiological effect. Thus, blockade of the NMDA receptor or nitric oxide synthesis has long been suggested to be a useful approach in treating pain, particularly neuropathic pain. Our studies with the rat model indicate that this may indeed be the case. Hence, we have shown that three NMDA receptor antagonists, MK-801, CGS 19755 and dextromethorphan, and two nitric oxide synthase inhibitors, L-NAME and 7-nitro indazole, are fully effective in alleviating allodynia-like behaviours in spinally injured rats (33, 34). However these compounds produced various side effects at effective doses. In the clinic, where several commonly used drugs have NMDA receptor blocking properties such as ketamine, dextromethorphan and memantine, side effects on cognition, attention and memory have also been consistently observed (35). Thus, future application of NMDA receptor antagonists in analgesia may depend on the development of receptor sub-unit specific drugs as well as drug combinations.

Others

Tricyclic antidepressants are increasingly popular in the management of neuropathic pain, including SCI pain. No controlled studies have been published, however, on its efficacy in SCI pain (23) and we are not aware of experimental studies using antidepressants in animal models of SCI pain.

In a series of studies, we used our model of SCI pain to study a novel approach in producing analgesia, namely i.t. implantation of bovine chromaffin cells which release analgesic substances such as catecholamines and enkephalins. We showed that i.t. chromaffin cells either in free form or in encapsulation provide long lasting alleviation of chronic allodynia-like behaviours, indicating a possible clinical application of this method in treating neuropathic pain (36, 37).

CONCLUSIONS

Significant advances have been made in the development of clinically relevant animal models for pain following SCI (4, 5). Although there have been no ground-breaking developments in treatment resulting from studies on animal models so far, considerable knowledge has been gathered of the physiology and pharmacology of this pain condition. The accumulation of such knowledge will likely contribute to the quest for effectively treating SCI pain, a task that has largely eluded pain management so far.

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