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Review paper

Central Pain : an overview

Jacques DEVULDER, Erwin CROMBEZ and Eric MORTIER
Department of Anaesthesia-section Pain Clinic, Ghent University Hospital, Ghent, Belgium

Abstract

Central pain is a particular form of neuropathic pain. Due to lesions in the spinothalamocortical pathways, ectopic neuronal discharges can occur into different neurons of the spinal cord and brain. Functional MRI, and positron emission tomography might be able to visualize ongoing pain activity which is, sometimes the consequence of spinothalamocortical lesions. Sometimes the patient experiences a burning ice-like sensation. This is more frequent in spinal cord lesions than in brain injuries. Some adrenergic, gabergic neurotransmitters, glycine, prostanoids and glutamate may play a role in pain transmission. These transmitters can induce changes in the neuronal membrane potential.

Consequently, amitriptyline as an adrenergic reuptake inhibitor and the sodium channel blockers are the drugs of first-choice. A test procedure with placebo, opioids, lignocaine, propofol and ketamine might give some insight into advanced drug treatment. If oral or transdermal drug delivery is not indicated or ineffective, the intrathecal administration route can be attempted with baclofen, clonidine, opioids and midazolam. Invasive electrostimulation is the last treatment option. Thalamic stimulation can be tried in spinal cord injuries, and sensory motor cortex stimulation is sometimes the last resort for brain lesions associated with pain.

Key words : Central pain ; anticonvulsants ; neuromodulation ; drug testing ; intrathecal drugs.

Introduction

The International Association for the Study of Pain (IASP) defines pain as " an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"(17). Particular pain descriptors enable physicians to discriminate nociceptive from neuropathic pain (18). Nociceptive pain is mainly the result of tissue damage and is described by the patient as aching, gnawing, stabbing, stinging… This pain becomes more pronounced by pressure and body movements when nociceptors become more excited. Neuropathic pain is the result of nerve tissue damage. Burning, shooting, splitting, tiring pain is frequently experienced by the patients. Neuropathic pain constitutes a difficult therapeutic challenge.

Neuronal excitation starts at the nerve and includes the spinal cord and the brain. Disorders of peripheral nerves and nerve roots give rise to peripheral neuropathic pain. Usually, treatment is more effective in peripheral neuropathic pain than in pathological conditions of the central neuraxis. Especially neuropathic central pain will discussed.

Central pain - etiology

Two etiologies causing central pain can be distinguished : lesions of the spinal cord by trauma or disease and brain tissue disorders (41, 43).

Any lesion somewhere along the spinothalamocortical pathways can induce central neuropathic pain.

Burning pain is a frequently described sensation although ice-like, tingling, shooting, tiring and bursting sensations are also reported (43, 8). Sensory testing of the referred pain area frequently shows a paradoxical hypoalgesia when nonpainful pinprick stimuli are delivered or an evoked potential examination is performed (6, 9, 15, 24). Often, the referred painful body area feels cold because of autonomic impairment (9, 20).

Central pain is estimated to occur in 2 to 8% of all stroke patients. Thalamic lesions are seen in 20% of them (2). Any lesion either by infarction, bleeding or injury to the dorsal horn, ascending pathways of the spinal cord, brainstem, thalamus, subcortical white matter and cerebral cortex can induce neuropathic central pain. However, it is more common in dorsal horn and spinal cord lesions, where 25 to 40% of the patients experience pain (20).

Pathophysiology

It is very important for physicians to have knowledge about the pathophysiology of central pain, not only to understand the patients' complaints but also to inform and to assure them that their complaints are taken seriously. Indeed, physiological mechanisms are very complicated as many excitatory and

inhibitory neuronal mechanisms are involved in the generation of pain. Ectopic neuronal discharges send information to the cortical sensory area giving the patient the illusion of noxious input (21). This neuronal firing occurs spontaneously or is induced by innocuous input such as cold, warm or pressure stimuli applied to the peripheral hypoalgesic area. These pain and temperature stimuli are transmitted along the different laminae neurones towards the controlateral spinothalamocortical system. Many stimuli are projected to the thalamic nuclei as : VMpo, MD vc, and VPI from where they are transmitted to the dorsal anterior insula, area 3a of the SI cortex or area 24c (Fig. 1) (48).

Animal studies suggest that these innocuous signals induce pain because of an imbalance between the integrity of the lateral and median spinocorticothalamic pathways (16, 31). The lateral pathway is rather inhibitory and the median is excitatory. This explains why pain occurs more frequently in incomplete lesions than in complete cord and thalamic injuries. If destruction is complete, neither inhibition nor excitation occurs. The onset of pain after the lesion is another confounding feature (5, 9, 43). In some patients pain onset is noticed immediately while in others it is delayed. The latter finding is explained by secondary insults or degeneration of various neuronal structures. This is only speculative as up - or downregulation of neurons is an alternative explanation for delayed pain onset (43).

Physiological mechanisms can differ from patient to patient, as is illustrated by varying clinical quantitative sensory test results, when cold, warm and pressure stimuli are applied in identical lesions. Moreover, differences are visualized by functional magnetic resonance imaging (fMRI), positron emission tomography (PET) or single photon emission computed tomography examinations(SPECT) (10, 23, 30, 42). These techniques demonstrate the activation of several areas in the brain when cold stimuli are delivered while the patient feels a more pronounced burning sensation. Thalamocortical areas and nuclei in the limbic system are lightening up by evoking painful sensations. It remains very difficult to describe specific pain centres but it noticed that also many extrathalamic pathways are involved. They include the spinohypothalamic tract, the spinoreticular tracts, the spinoparabrachioamygdalar pathway, the direct spinolimbic tracts. It is not the purpose of this review to discuss these pathways in detail. This pain is not only induced by spontaneous ectopic excitation of some median thalamic nuclei or even pathways into the white matter, but also by excitation of the centres where integration of thermosensory and pain- related activity is modulated. Indeed, in mammalians regulation of pain and maintenance of temperature is essential for homeostasis and survival. If all neuronal structures function properly, pain and temperature information are in proportion to body reactions (20).

However, if some anatomical structures are injured, excitation and disinhibition occur with the consequent unrealistic sensations. The autonomic reactions with vasoconstriction in the referred pain area are produced by central stimulation of the sympathetic system (19).

Excitation and inhibition of neurons occur by neurotransmitters such as glutamate, gamma aminobutyric acid, glycine,norepinephrine, prostanoids, substance P, adenosine and many others. These transmitters excite neurons by changing their membrane potential through voltage gated sodium and calcium channels (37). The influx of sodium and calcium initiates action potentials. The outflow of potassium is a nervous protection system to reduce pain. Unfortunately, the latter is disturbed in nervous tissue lesions so that pain transmission is enhanced (33).

Pain treatment strategies

Chronic pain behaviour is a complex phenomenon produced by sensory, autonomic, muscular, cognitive and affective input. When treatment is considered a cognitive behavioural psychological intake seems worthwhile. After the diagnosis has been made adjuvant cognitive behavioural treatment can be started. Moreover, psychological screening can give us information as to whether more invasive treatment is feasible or not advisable.

Medical treatment

a) Amitriptyline, inhibiting the central reuptake of serotonine and adrenaline, in an oral daily dose of 25 tot 75 mg, can modulate neuropathic central pain. Sedation reducing quality of life can occur, so that amitriptyline treatment has been abandoned. However, sedation ultimately weans off in the majority of patients. On the other hand, the anticholinergic side effects are an absolute contra-indication for amitriptyline treatment in patients with glaucoma, cardiac arrhythmias and prostate gland hypertrophy (34, 36).

b) In neuropathic pain alpha 2 receptors can extensively be expressed along the affected nerve pathway. They play a part in sympathetically maintained pain. Central neuropathic pain can also enhance sympathetic activity. Consequently, clonidine, an alpha 2 agonist given orally or intrathecally, can have beneficial effects on neuropathic pain. A daily dose of 150 µg to 300 or even 600 µg can be administered (40). Sedation and low blood pressure are frequently noticed.

Sympathetically maintained pain can also be treated more invasively by sympathetic ganglion blocks (46). If the diagnostic block only alleviates

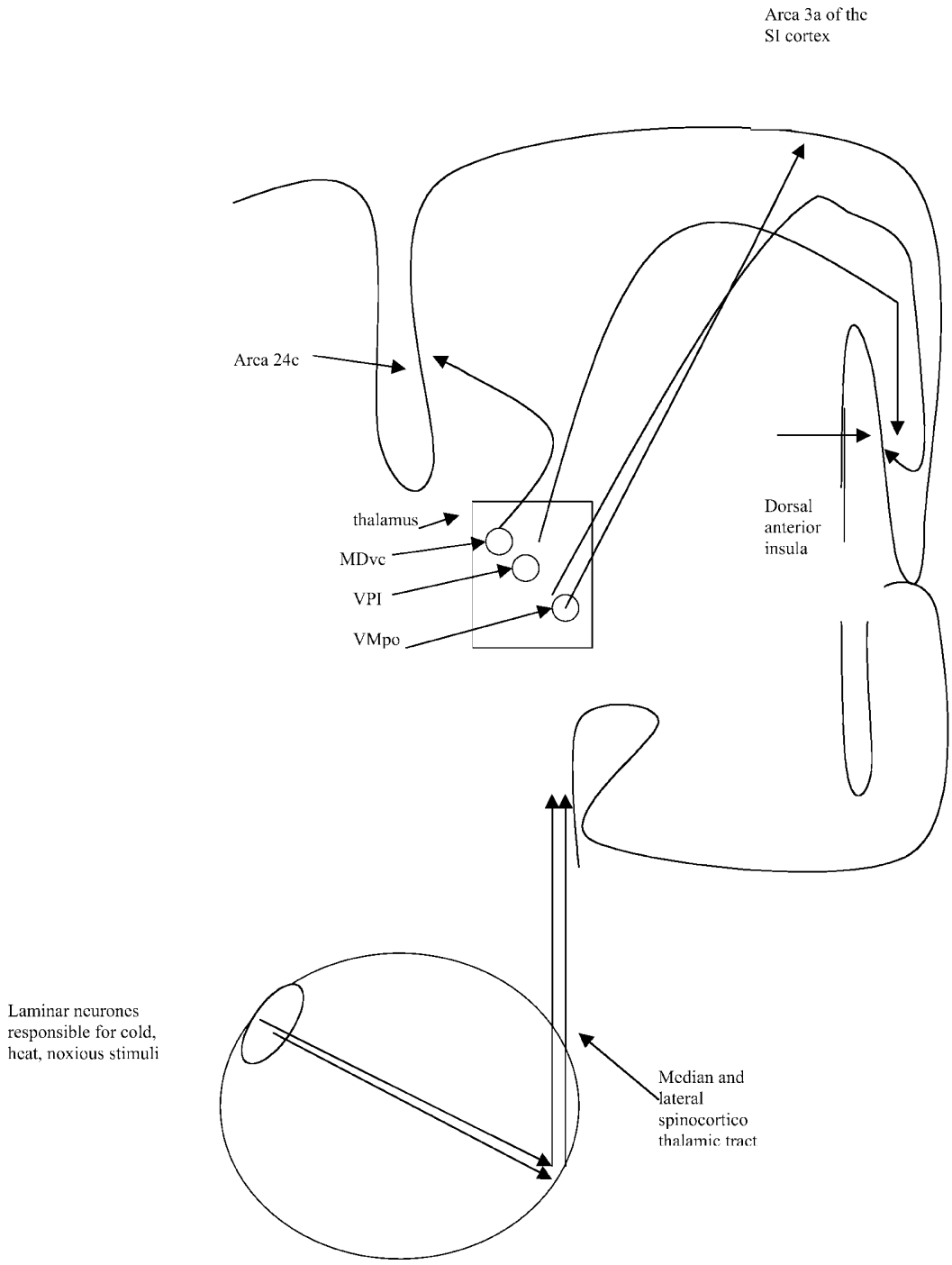

FIG. 1. — Proposed spinocorticothalamic pain pathway

pain for a short time, radiofrequency lesions in the sympathetic ganglia can provide longlasting pain relief. The mechanisms explaining the effect of sympathetic blockade and pain relief are still speculative but the hypothesis of alpha adrenergic sensitivity after injury is still maintained (26).

c) Depending on the physiological mechanisms an intravenous test using different drugs can be performed, in an attempt to obtain pain relief by one or another drug or combination of drugs.

Neuronal excitation by sodium influx is an important mechanism in pain transmission. Obviously, sodium channel blockers are an option to block the tetrodoxin- sensitive voltage gated sodium channels. In the absence of cardiological contraindications lignocaine can be infused intravenously or subcutaneously (26). After a positive lignocaine test, the antiarrhythmic drug mexilitine can be started (32). If the lignocaine test is negative, sodium channel blockers such as the anticonvulsant carbamazepine, phenytoine or sodiumvalproate can be instituted (31). Dizziness, somnolence and trembling sometimes limit or even lead to cessation of treatment.

d) Canavero reported a treatment scheme for central pain and suggested carbamazepine as a

sodium channel blocker (13). Carbamazepine can alleviate pain by blocking tetrodoxin-sensitive sodium channels. However, in neuropathic pain tetrodoxin- resistant sodium channels are expressed so that many voltage gated tetrodoxin- sensitive sodium channel blockers are ineffective. Newer anticonvulsants such as lamotrigine, gabapentin or topiramate block tetrodoxin-sensitive as well as tetrodoxin- resistant sodium channels. Some of them also have N-methyl dextro aspartate (NMDA) receptor-blocking activities.

e) In chronic pain NMDA receptors greatly contribute to the maintenance of pain stimuli and sensitization (49). NMDA receptors are normally blocked by a magnesium ion. However, by continuous glutamate release, the magnesium block is lost so that sodium and calcium influx is enhanced, evoking further neuronal excitation. In humans the search for NMDA receptor-blocking agents is still going on. Ketamine seems the most appropriate as it is the most potent NMDA receptor antagonist with the smallest side effect profile (4). In higher doses lamotrigine, gabapentin and topiromate also show some NMDA receptor antagonism (13). As sensory excitation occurs by influx of sodium and calcium ions, the mammalian body protects itself against pain by potassium ion outflow.

f) However, in neuropathic pain potassium channels remain in a locked position, limiting potassium release. Flupirtine is a drug acting by SNEPCO (Sensory Nerve Potassium Channel Opener). By this mechanism flupirtine can protect nervous tissue against apoptosis or excessive neuronal discharge. Consequently, it can be used as an analgesic in central pain (300-600 mg/day). Somnolence is sometimes noticed and can limit treatment (35).

Gabapentin is probably the most selected anticonvulsant to treat neuropathic pain and central pain. Its small side effect profile, having no metabolites and little interference with concomitant drug metabolism, makes it an attractive drug (45).

g) Theoretically, opioids are not the first drug to treat neuropathic pain. Indeed, in neuropathic pain opioid receptor expression is downregulated, so that opioid analgesia becomes less effective (22). However, since central opioid receptors remain present in the spinal cord and brain, an intravenous trial with alfentanyl can be performed. If positive, physicians can try oral treatment with strong opioids such as slow-release morphine or transdermal fentanyl (13).

h) Intravenous ketamine is the object of another screening procedure to establish whether glutamate and the NMDA receptors are involved (6 µg/kg/min) (25). A positive response may lead to continuous subcutaneous or central intrathecal infusion. However, neurotoxicity and hepatic toxicity are not excluded (1).

Oral lamotrigine could be an alternative drug. Lamotrigine is a voltage gated sodium channel blocker, probably also with calcium channel-blocking activity and NMDA receptor antagonism (12). Unfortunately, lamotrigine is expensive and not reimbursed for pain therapy in many countries. Moreover, it must be titrated very slowly during the first six weeks of treatment to prevent a toxic rash. Pain reduction usually occurs at oral dosages of more than 200 mg lamotrigine daily (38).

Intrathecal treatment

As oral or transdermal opioids are not directly applied to the central neuraxis they are less effective than the intrathecally administered opioids. A properly placed intrathecal catheter at the level of the lesion or more cranially gives the opportunity to administer the opioid closer to central opioid receptors, which can better desensitize the excited neurons. These opioids act by activating a G protein blocking sodium and calcium channels. Moreover, opioids can also prevent glutamate release, an excitatory amino acid.

Intrathecal drug therapy is always attempted with an external pump for some weeks. Finally, after a positive trial, a programmable electronic pump can be implanted and connected with the intrathecal catheter.

Gamma aminobutyric acid (GABA) is another neurotransmitter controlling neuropathic central pain. Intravenously infused propofol, also a GABA-a agonist, may relieve both spontaneous and evoked components of central pain in subhypnotic doses (0,2 mg/kg) (11, 13). If the intravenous test is positive one can expect to obtain pain relief by intrathecal baclofen and/ or midazolam or the combination of both. As described with intrathecal opioids, a positive trial running over several weeks is mandatory before pump implantation. The catheter tip should also be placed near the lesion level for spinal disorders and the baclofen dose should be titrated very carefully, as baclofen can induce profound sedation and even spinal shock when inadvertent overdose occurs. A positive intravenous propofol test is also an indication for intrathecal midazolam instillation (7). Intrathecal midazolam neurotoxicity has long been the subject of much debate. Nowadays we can assume that midazolam is not neurotoxic provided that no preservatives are suspended into the solution. Midazolam is sometimes instilled intrathecally with either baclofen, clonidine, morphine or bupivacaine (47).

Electrical Nerve Stimulation

If all treatments fail to significantly reduce neuropathic pain, more invasive treatment is an option. However, such treatment should be carefully

considered and patient screening is essential. Pain and neuropathic central pain are biopsychosocial events and have many components explaining the severity of pain. This is well documented by the ring diagram of Loeser (44). Consequently, prior to invasive treatment a psychosocial evaluation should be performed. Cognitive behavioural treatment can be helpful in many of these patients and prevent failure of drug treatment, invasive electrostimulation or spinal analgesia delivery (29).

Electrical stimulation of specific brain structures and intrathecal drug instillation are invasive procedures.

Intrathecal drug instillation has already been explained and will for this reason not be repeated.

1°) Transcutaneous electrical nerve stimulation will be insufficient in the majority of patients as input of the electrical pulses will be absent because of hypoalgesia or even anaesthesia (27). Furthermore, as described in the gate control theory, substantia gelatinosa cells, which normally reduce pain input, are absent in spinal cord or brain injury, and their function can be changed by neuroplasticity turning them into excitatory instead of inhibitory cells. In these conditions neither transcutaneous nerve stimulation nor spinal cord stimulation will induce pain relief (28).

2°) In these patients electrical stimulation of the thalamic structures, inducing paresthesias in the referred pain area, can alleviate pain. This can be helpful for spinal cord lesions. Implantation of the stimulator is recommended after good pain relief has been achieved during a minimal test period. Obviously, thalamic stimulation will not be helpful

Treatment flow chart of neuropathic central pain

1) intake patient (physician) + psychosocial intake

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if possible cognitive behavioural treatment

drug treatment a) amitriptyline 25-75 mg / daily (first choice)
b) sodiumvalproate or carbamazepine or phenytoine (second choice)

2) If insufficient relief :
Intravenous test

Saline
↓

↓ ↓

\+ –

stop treatment lidocaine test

↓

– + → start oral mexiletine

↓

iv clonidine

↓

\- – + → oral clonidine → –

↓

sympathetic ganglion block

–

↓

alfentanyl test

↓ ↓

+ oral transdermal opioid – propofol test

↓ ↓

– IT spinal opioid + IT baclofen and midazolam –

↓ ↓ ↓

– – ketamine test

↓

– + ketamine
lamotrigine

↓ ↓ ↓

consider 1) thalamic neurostimulation
2) motor cortex stimulation

for lesions in the thalamus or higher in the white matter or cerebral cortex. Whenever the thalamus or higher pain regions are damaged only sensory-motor cortex stimulation can be attempted (14).

As explained in the pain physiology, central neuropathic pain signals can be visualized by functional MRI (28). The typical cortical areas can be properly determined and some investigators have tried to treat central neuropathic pain by using epidural motor cortex stimulation. Good results have been obtained, although it is not well understood how motor cortex stimulation can alleviate pain in the leg, back and arm. Motor cortex stimulation for central neuropathic pain might also induce epileptic attacks but these have not been described in the long-term evaluation (39). This treatment approach is presented in a flow chart (see above).

Conclusion

Central pain is more common in spinal cord injuries than in brain damage. Patients can complain of different symptoms although a burning, ice-like sensation is frequently reported. As for every complex pain pathology a rigorous intake with psychosocial evaluation is mandatory. Adjuvant cognitive behavioural therapy can be beneficial in these difficult pain syndromes. Drug treatment with amitriptyline or anticonvulsants can be started. If pain relief is insufficient, intravenous drugs can be tested to initiate oral, transdermal or intrathecal treatment either with these drugs or with equivalents. Electrical stimulation of the thalamus or sensory-motor cortex is a more invasive treatment option.

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J. DEVULDER, M.D., Ph.D.,
Ghent University Hospital -Pain Clinic,
De Pintelaan 185,
B-9000 Ghent (Belgium).
E-mail : jacques.devulder@rug.ac.be.