International Journal of Enhanced Research in Medicines & Dental Care, ISSN: 2349-1590
Vol. 3 Issue 9, September-2016, Impact Factor: 1.102

Neural mechanisms of contemporary alternative analgesic modalities: a mechanistic context for Marma Cikitsa

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ABSTRACT

Background. The mechanism of Marma Cikitsa remains obscure and may overlap with several contemporary alternative analgesic therapies, justifying a careful review of those therapies whose mechanisms are better characterized. **Scope.** This paper synthesizes the chapter "Review of Contemporary Alternative Therapies" and surveys five modalities cited there: acupuncture analgesia (manual and electroacupuncture), offset analgesia, diffuse noxious inhibitory control (DNIC), stress-induced analgesia (SIA), and manipulation-induced analgesia. **Key mechanisms.** Acupuncture analgesia is shown to depend on activation of muscular and connective-tissue afferents (Aβ, Aδ and C fibers), spinal pre- and post-synaptic inhibition, and a distributed supraspinal network involving PAG, RVM/NRM, ACC, hypothalamic and limbic nuclei, with endogenous opioids, CCK-8, 5-HT, noradrenalin, glutamate, GABA, Substance P and dopamine implicated. Offset analgesia and SIA likewise engage descending PAG–RVM circuits, with offset analgesia distinguished from DNIC by its time-locking to stimulus reduction. DNIC involves a spino-bulbo-spinal loop centered on the subnucleus reticularis dorsalis with partial opioid sensitivity. Manipulation-induced analgesia is largely non-opioid, depending on segmental gate-control mechanisms, GABAergic spinal inhibition, and serotonergic/noradrenergic descending pathways. **Conclusion.** The review presents the parallels with acupuncture analgesia and DNIC most explicitly, while drawing no direct mechanistic equivalence between Marma Cikitsa and offset analgesia, stress-induced analgesia, or manipulation-induced analgesia. Shared anatomical substrates — particularly the PAG–RVM axis and the same brainstem and limbic targets implicated across the five modalities — provide a candidate framework, but, as the review itself notes, the mode of action of Marma Cikitsa is hypothesised in light of current modern knowledge and contemporary therapies rather than established by direct experimental work in the Marma Cikitsa setting.

1. INTRODUCTION

There are many alternate therapies similar to Marma Cikitsa, a quite famous example being acupuncture, and it is unwise to ignore them while addressing Marma Cikitsa because its mechanism remains obscure and may overlap with present alternative therapies. The chapter under review identifies five such therapies: acupuncture analgesia (manual and electroacupuncture variants), offset analgesia, manipulation-induced analgesia, and stress-induced analgesia, with diffuse noxious inhibitory control (DNIC) treated as a closely related counterirritation phenomenon. Each has been investigated through animal experiments, human psychophysics, neuroimaging and pharmacology, and each has been linked, with varying certainty, to descending pain-modulatory pathways anchored in the periaqueductal gray (PAG) and rostral ventromedial medulla (RVM). Because these therapies engage circuits that may be common to several non-pharmacological interventions, the chapter argues that they form an essential context for understanding Marma Cikitsa. The present review consolidates the chapter's account of peripheral, spinal and supraspinal mechanisms, the principal neurotransmitters and modulators, and the points at which the review itself acknowledges contradictory or fragmentary evidence. Faithfulness to the review is preserved throughout, and gaps are reported rather than filled.

2. ACUPUNCTURE ANALGESIA

Acupuncture has been a Chinese healing art for over 2000 years; its analgesic application — "acupuncture analgesia" — is used for diverse pains, particularly chronic pain. Acupoints lie along meridians ("Jing") and their branches ("Luo"), with 361 acupoints classically described, and traditional theory holds that pain reflects a meridian blockade purged by

acupuncture to restore "Qi." No convincing evidence has demonstrated novel anatomical meridian structures; meridians may be functional rather than anatomical. [79]

2.1 Peripheral mechanism

Clinical practice emphasizes the "needling feeling," De-Qi — soreness, numbness, heaviness and distension beneath the acupoint, with a pulling sensation in the acupuncturist's fingers. Lower-limb needles failed to produce De-Qi or upper-body analgesia in paraplegic patients. Morphological work showed 323 of 324 acupoints richly innervated in deep tissues, with lower subcutaneous nerve density at acupoints than at non-acupoints; skin afferents are not crucial. A- and C-fiber receptive fields concentrate at acupoints or along meridians, suggesting excitable muscle/skin nerve complexes. Impulses originate predominantly from muscle, with deep-tissue polymodal receptors central. Of two patients with congenital insensitivity to pain, one with intact deep sensation retained needling feeling, the other did not. Needle–connective-tissue mechanical coupling is also implicated: ST-36 acupuncture enhanced mast-cell degranulation, and chromoglycate destruction of mast cells weakened the analgesia.

Electroacupuncture (EA) at intensities exciting Aβ afferents (group II) produces analgesia, with Aδ (group III) excitation more potent. Recruitment of the whole A-type spectrum inhibits dorsal-horn nociception more than Aβ alone, with Aβ amplitude correlating with suppression of the rat jaw-opening reflex. Partial Aδ excitation produces an acceptable EA sensation. EA induces Fos via capsaicin-insensitive afferents, presumably Aδ; surface electrodes activate the same fibers.
Manual acupuncture (MA) at LI-4 (Hegu) raises the pain threshold; muscle-nerve, but not skin-nerve, blockade abolishes the effect. De-Qi requires repetitive twirling that may injure muscle, releasing histamine, bradykinin, PGE2, 5-HT and ATP; C-fibers therefore contribute, supported by feline work. Capsaicin blockade of Aδ and C afferents abolished MA analgesia, paralleling DNIC. EA and MA differ in fiber preference — Aβ/δ for EA, all types and especially C for MA — and combined EA plus MA is more potent than either alone. [79]

2.2 Central mechanisms

Acupuncture analgesia outlasts needling, indicating central summation: any innocuous sensory input may inhibit pain, with acupuncture-evoked impulses being especially effective. It is an integrative process at multiple CNS levels. The strongest spinal inhibition occurs when acupoint and painful receptive field share a nerve, and EA at ST-36 reduces noxious-thermally evoked Fos in superficial dorsal horn in rat neuropathic pain, supporting segmental specificity; many distant acupoints are also effective. Synaptic analysis shows pre- and post-synaptic inhibition: EA depolarizes primary C-afferent terminals, reducing substance P and glutamate release, and inhibits sympathetically mediated dorsal-root impulses; EA at ST-36 produces IPSPs and long-lasting hyperpolarization in cat dorsal-horn nociceptive neurons. Impulses ascend mainly through the ventrolateral funiculus.[79]

Many supraspinal structures participate — RVM (mainly NRM), PAG, locus coeruleus, Arc, Po, CM, Sm, APtN, Hab, Ac, Cd, Sp, amygdala, ACC and PVH; stimulation of these (except Hab) potentiates EA analgesia and lesions attenuate it. Several schematics have been proposed. Functional imaging shows acupuncture activates PAG and NRM and deactivates limbic regions including insula and ACC; ACC is also implicated in descending facilitatory modulation.

2.3 Transmitters, modulators, glia and molecular note

Endogenous opioids are central. EA raised β-endorphin-like immunoreactivity in ventricular CSF of brain-tumour patients, lumbar CSF of chronic-pain patients, and rabbit PAG. Naloxone blocked EA inhibition in cat dorsal horn and reversed EA analgesia in monkey, with conflicting human results; CXBK opiate-receptor-deficient mice showed poor EA analgesia, and peptidase inhibitors potentiated it. Peripheral opioids are also implicated: intraplantar naloxone methiodide eliminated the EA effect in CFA inflammation, and intraplantar β-endorphin antibody or CRF antagonist reduced EA analgesia. Supraspinal opioid-receptor blockade in Sm, Cd, Sp, Ac, Arc, PAG and NRM diminishes acupuncture analgesia, consistent with an Arc–PAG–NRM–dorsal-horn pathway; EA produced naloxone-reversible inhibition in opioid-rich anterior thalamic nuclei (AD).

CCK-8 acts as an anti-opioid, and CCK-receptor blockade potentiates placebo analgesia, itself opioid-mediated, so EA may share an opioid mechanism with placebo. 5-HT1A and 5-HT3 subtypes mediate EA analgesia through substance P modulation; noradrenalin inhibits acupuncture analgesia in brain nuclei but potentiates it spinally; EA with NMDA or AMPA/KA antagonists yields synergistic anti-nociception against inflammatory pain. GABA's role in pain is well established [1] but remains obscure in acupuncture analgesia. Dopamine antagonists potentiate EA and up-regulate opioid receptors in Cd, Po, PVH and PAG; D1 activity may reduce EA analgesia.

Spinal microglia and astrocytes contribute to inflammatory and neuropathic pain. EA at GB30 and GB34 reduced hyperalgesia and allodynia in monoarthritic rats, and intrathecal fluorocitrate plus EA potentiated the effect. Molecular mechanisms remain preliminary.

3. OFFSET ANALGESIA

Interrupting a continuous noxious heat with a greater noxious heat causes rapid and disproportionate pain reduction when the original heat returns; this offset analgesia is believed to reflect active descending inhibitory control from PAG and RVM. It exemplifies how stimulus manipulations induce adaptive plastic changes in the nociceptive system, paralleling concurrent-stimulus DNIC paradigms [2, 3]. PAG electrical stimulation permits surgery without further analgesia, and descending modulation is localized to the RVM. The PAG–RVM–spinal cord pathway is the essential opioid-based pain-inhibition circuit, with intra-PAG opioid agonists producing naloxone-reversible analgesia and RVM excitation. The rapidity and magnitude of offset analgesia are consistent with engagement of this circuit. fMRI shows offset engages an inhibitory system originating in ventrolateral PAG involving brainstem nuclei consistent with serotonergic and noradrenergic systems, and animal studies indicate an age-related decline in serotonergic and noradrenergic dorsal-horn neurons that impairs descending inhibition.

Offset analgesia is spatially localized — spatial summation was not observed when two probes simultaneously delivered offset-inducing stimuli. Selective inhibitory interconnections of the substantia gelatinosa could support such localization, with islet cells providing a restricted route by which large-diameter C-fiber afferents inhibit small-diameter C-fiber effects on central cells. Supraspinal mechanisms involving PAG may also contribute [1], with imaging showing transient PAG activation following incremental decreases in stimulus intensity, and ON/OFF cells in the medullary NRM may participate. Localized endogenous effects also appear in placebo analgesia. Offset analgesia is distinct from DNIC: it is time-locked to stimulus offset, whereas DNIC is activated by the onset of a remote noxious stimulus [2–4].

4. DIFFUSE NOXIOUS INHIBITORY CONTROL (DNIC)

DNIC is the strong inhibition of dorsal-horn neurons when a nociceptive stimulus is applied to any body part distinct from their excitatory receptive fields [5, 6]; behaviorally it manifests as decreased pain during or following another noxious stimulus elsewhere — the counterirritation principle that pain inhibits pain. Various noxious modalities (thermal, mechanical, electrical, ischemic, chemical) produce remote analgesia in humans [7–14]. Animal studies show inhibition of spinal [2, 15–18] and trigeminal wide-dynamic-range neurons [19–21] outside the excited segmental dorsal horn [22]. Rat lesion studies identify a supraspinal loop emanating from the subnucleus reticularis dorsalis in caudal medulla [3, 4, 6, 17, 22, 23], and rodent work implicates serotoninergic, opioidergic, dopaminergic and neurokinergic systems [5, 24–29].

Human imaging has only partially characterized DNIC. One fMRI study reported decreased SI, ACC, PFC and amygdala activity during analgesia to electric shock at the right ankle produced by cold-water immersion of the left foot [30]; the counterirritation stimulus itself activated SI, ACC, anterior insula (aINS), PFC, OFC, midbrain (PAG) and pons, consistent with the pain neuromatrix and descending modulation. Reductions in ACC, PFC and amygdala were interpreted as endogenous opioid release [30, 31], and ipsilateral OFC activity scaled with analgesia and covaried with amygdala activity, suggesting cortico-amygdaloid regulation of opioid release [30, 31]. Another study reported bilateral SI, ACC (BA24, BA32) and PFC activation during reduction of pain to rectal balloon distension following a cold-pressor task [32], with reductions in anterior/posterior insula, medial thalamus and PAG; OFC was not activated [33, 34]. A further fMRI study using right-leg cold-pressor during left-arm phasic heat reported reductions in contralateral thalamus, bilateral SII, anterior/posterior insula, cingulate cortex, bilateral amygdala and medulla [35]. Greater analgesia correlated with reduced activity in right thalamus, left insula, dorsolateral PFC and dorsal medulla. Naloxone reduced but did not abolish these correlations and lessened DNIC activation of SII, amygdala, PAG/midbrain and OFC, while leaving subjective pain unaffected, suggesting an indirect role for the PAG-opioidergic system. The same study found enhanced coupling between subgenual ACC (sACC) and PAG/midbrain, left amygdala, hypothalamus and medulla during DNIC, with strength correlating with analgesia and diminished by naloxone for sACC–PAG/midbrain and sACC–left amygdala, supporting a pain-modulatory role of the ACC.

Collectively, human studies show reduced activity during DNIC in SI, ACC, PFC, amygdala, insula and thalamus, with PAG–RVM and ACC involvement. PAG activations may reflect concurrent stress-induced analgesia [33] or attentional shifts. Most animal studies hold DNIC to rely on a largely independent spino-bulbo-spinal loop with minimal input from the PAG–RVM axis.

5. STRESS-INDUCED ANALGESIA (AND STRESS-INDUCED HYPERALGESIA)

Stress-induced analgesia (SIA) is an in-built mammalian pain-suppression response during or following stressful or fearful stimuli, plausibly redirecting attention to more urgent matters [36]. The endogenous opioid system is the best-established mediator, but GABAergic, glutamatergic, cannabinergic and monoaminergic systems are also implicated [36, 37]. RVM, PAG and amygdala lesions weaken SIA [37, 38], the amygdala being especially activated by stress and fear [39], and amygdala neurons project to brainstem PAG and raphe nuclei, which project to the dorsal horn [36, 40, 41]. Human imaging confirming this circuitry is currently lacking.

The intensity, duration and type of stressor appear to determine the form and degree of SIA. Sequential inescapable foot shocks in rats produced both early naltrexone-insensitive and late naltrexone-sensitive analgesia [42, 43]. In a forced swim test, SIA increased with more extreme temperatures [44], and degree varied with shock frequency and pulse-width [45]. Under some conditions stress induces hyperalgesia [46]; this stress-induced hyperalgesia may be related to anxiety-induced hyperalgesia and is poorly differentiated in the literature. Like SIA [47, 48], it involves serotonin [49, 50], with effects depending on receptor subtype: 5-HT2/3/4 enhance neuronal activity, 5-HT1A/1B suppress it [1], and dorsal-horn 5-HT receptor location on excitatory or inhibitory interneurons further shapes outcome. Opioid-receptor overactivation and desensitization may also contribute during prolonged stress [51–54]. Neuroimaging of stress-induced hyperalgesia is scarce; the only study identified found chronic stress correlated with activity in right posterior insula, right dorsal posterior cingulate, right PAG and left thalamus during rectal balloon distension in healthy females [55], consistent with stress contributing to chronic pain conditions such as fibromyalgia and irritable bowel syndrome [56, 57].

6. MANIPULATION-INDUCED ANALGESIA

Joint manipulation has long been used for pain relief, evolving from bonesetting into orthodox practice; modern techniques range from low-oscillating glides to high-velocity, low-amplitude (HVLA) thrusts, with manipulation defined as HVLA thrusts and mobilization as lower-velocity passive movements [58]. Manipulation-induced analgesia has been demonstrated in human studies [59, 60], and meta-analyses suggest spinal manipulation is effective for acute and chronic musculoskeletal pain. Cervical manipulation increases active range of motion and decreases neck pain [61–64]. The mechanisms are multifactorial — effects on the peripheral joint chemical environment, tissue repair, segmental CNS inhibition, and descending inhibitory activation.

Spinal manipulation may induce reflex pain inhibition or muscle relaxation via joint-capsule mechanoreceptors or muscle spindles [65, 66], alter inflammatory mediators [67], or trigger segmental inhibition [68]; opioid involvement has also been suggested [62, 69]. Manual mobilization induces mechanical, but not thermal, hypoalgesia [70], and this effect is non-opioid — not reversed by naloxone [71] and without tolerance to repetition [72]. Mechanical hypoalgesia is concurrent with sympathetic [59, 73] and motor [74] excitation, supporting descending inhibitory contributions [68, 75, 76]; animal-joint work shows it involves spinal serotonin and noradrenaline receptors [77].

Local effects [74] may reflect stimulation of large-diameter low-threshold mechanoreceptors at the spinal cord [77], consistent with gate-control theory [78]; manual procedures may also reduce joint afferent activity [75]. Knee-joint manipulation decreased secondary mechanical hyperalgesia in the rat paw after capsaicin injection in the ankle; central mechanisms appear responsible. Presynaptic GABA receptors on primary afferent terminals depolarize them and reduce transmitter release, and post-synaptic GABA receptors hyperpolarize neurons. Opioids contribute to segmental and descending inhibition, but systemic naloxone has no effect on human manipulation-induced analgesia. Descending RVM pathways use serotonin and those from the dorsolateral pons use noradrenaline.

8. DISCUSSION

The five modalities reviewed converge mechanistically more than they diverge. Acupuncture analgesia, offset analgesia, DNIC, SIA, and manipulation-induced analgesia all engage descending modulatory circuits anchored in the PAG and RVM, although the balance of opioid and non-opioid components, the spinal substrates, and ascending afferent recruitment differ. Endogenous opioids dominate acupuncture and SIA, partially shape DNIC, and are dispensable for manipulation-induced analgesia, which is non-opioid and relies on segmental gate-control mechanisms and serotonergic/noradrenergic descending pathways. Shared dependence on deep-tissue mechanoreceptive and nociceptive afferents, with overlapping involvement of ACC, amygdala, insula and thalamic nuclei, makes these modalities a plausible mechanistic backdrop for Marma Cikitsa, whose mechanism the review repeatedly characterizes as obscure. The review proposes specific mechanistic parallels between Marma Cikitsa and the reviewed therapies that warrant explicit mapping. As with manual and electroacupuncture, it argues that Marma Cikitsa analgesia is essentially a manifestation of integrative processes at

different CNS levels between afferent impulses from the painful region and impulses from Marma points, with the spinal-segmental relationship between Marma site and pain locus paralleling the acupoint–pain segmental specificity already documented for acupuncture. The review further proposes that impulses from Marma points may ascend mainly through the ventrolateral funiculus — the spinal pathway of pain and temperature sensation — and that supraspinal processing engages the same constellation of nuclei recruited by acupuncture, including the RVM (mainly NRM), PAG, amygdala, ACC and PVH. With explicit reference to DNIC, the review suggests that Marma Cikitsa may activate PAG and NRM to engage descending inhibitory modulation while deactivating limbic regions linked to pain emotion. Endogenous opioids and serotonin are named as candidate inhibitory mediators, and Marma Cikitsa is framed as having a multidimensional effect across several pathways and systems rather than acting through any single mechanism.

These mappings remain hypothetical. The review presents the parallels with acupuncture analgesia and DNIC most explicitly, while drawing no direct mechanistic equivalence between Marma Cikitsa and offset analgesia, stress-induced analgesia, or manipulation-induced analgesia. Shared anatomical substrates — particularly the PAG–RVM axis and the same brainstem and limbic targets implicated across the five modalities — provide a candidate framework, but, as the review itself notes, the mode of action of Marma Cikitsa is hypothesised in light of current modern knowledge and contemporary therapies rather than established by direct experimental work in the Marma Cikitsa setting.

CONCLUSION

This review gathers evidence on the probable mechanisms of Marma Cikitsa, based on five alternate modalities being practiced which remain largely unclear. Across five modalities, findings suggest recurrent descending PAG–RVM modulation, varied opioid involvement, and common targets including the substantia gelatinosa, ACC, amygdala, insula, and thalamus, though no single mechanism explains all effects. For Marma Cikitsa, plausible hypotheses involve central summation, sensory interaction similar to acupuncture, spinal specificity, ascending pathways, and descending inhibition with limbic deactivation, partly mediated by opioids and serotonin. These are untested in this context. The review highlights molecular mechanisms of acupuncture analgesia, GABA's conflicting role, lack of imaging for stress-induced analgesia, and challenges with DNIC imaging as areas for further research. The review itself notes, the mode of action of Marma Cikitsa is hypothesised in light of current modern knowledge and contemporary therapies rather than established by direct experimental work in the Marma Cikitsa setting. Continued dialogue between pain neuroscience and Ayurveda, based on these substrates and acknowledging current gaps, is warranted.

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