The Neurophysiological Response to Manual Therapy and Its Analgesic Implications: A Narrative Review

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ABSTRACT

Manual therapy has long been a component of physical rehabilitation programs, especially to treat those in pain. The mechanisms of manual therapy, however, are not fully understood, and it has been suggested that its pain modulatory effects are of neurophysiological origin, and may be mediated by the descending modulatory circuit. Therefore, the purpose of this review is to examine the neurophysiological response of different types of manual therapy, in order to better understand the neurophysiological mechanisms behind each therapy's analgesic effects. It is concluded that different forms of manual therapy elicit analgesic effects via different mechanisms. Additionally, future avenues of mechanistic research pertaining to manual therapy are discussed.

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Introduction

Manual therapy has been a component of physical rehabilitation programs since as early as 400 BC (Pettman 2007). Since its inception, many variations of manual therapy techniques have been developed and marketed. Each year, upwards of $8.1 billion is spent in the US on manual therapies, including chiropractic/osteopathic manipulation and massage (Nahin et al. 2009). Despite the large annual financial expenditures on manual therapies, its mechanisms are not yet fully understood. Current research suggests that a neurophysiological response to manual therapy is responsible for clinically significant decreases in pain (Bialosky et al. 2009). Included in the neurophysiological response is the descending pain modulation circuit, which may be a principle mechanism in the analgesic effect of manual therapies.

Descending Modulation of Pain

Melzack & Wall (1965) were the first to explain the potential mechanisms of a central pain modulatory system, wherein the authors described the gate control theory of pain, which simply states that non-noxious input suppresses painful output by inhibiting dorsal root nociceptors. Numerous neurotransmitters, including serotonin (5-HT), endocannabinoids, and endogenous opioids (EO), have been shown to act on the rostral ventromedial medulla (RVM) and periaqueductal grey (PAG) in order to modulate nociceptive circuits and pain output (Adams et al. 1986; Benedetti et al. 2013; Fields et al. 1991; Mason 1999; Nadal et al. 2013; Ossipov et al. 2010).

β-endorphins are EO peptides that have not only been shown to have a comparable analgesic effect to morphine (Gerrits et al. 2003), but are 18 to 33 times more potent (Loh et al. 1976). Diffuse noxious inhibitory control (DNIC) is the process by which afferent noxious signals are inhibited from the peripheral nervous system (PNS). Using a rat model, Le Bars et al.

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(1979a); Le Bars et al. (1979b) found that neurons were inhibited by noxious stimuli (a hot bath), therein coining the term DNIC. Since then, multiple studies have suggested that EO are an underlying mechanism of DNIC (Chitour et al. 1982; Kraus et al. 1981).

Being that the analgesic effects of both human touch (Lindgren et al. 2012) and placebo (Colloca et al. 2013; Eippert et al. 2009; Morton et al. 2014; Sauro & Greenberg 2005; Wager et al. 2007; Zubieta et al. 2005) are mediated by an EO response, it is imperative that a placebo control group be utilized in research examining the neurochemical response to manual therapy, as placebo and touch alone are confounding variables. Previous reviews have noted potential descending modulatory mechanisms – an endogenous opioid response – in both physical therapy (Bender et al. 2007) and physical medicine (Crielaard et al. 1983); however, the neurochemical response to manual therapy and its implications for descending pain modulation, to the authors' knowledge, have not yet been thoroughly reviewed.

Manipulation Therapies

Through the millennia, numerous types of manipulation therapies have been developed and advocated, and have been purported to cure everything from scarlet fever and diphtheria to hearing loss (Pettman 2007). However, perhaps the most widely proclaimed outcome from manipulative therapy is pain relief, which may be modulated by neurochemicals that act on the RVM and PAG.

Osteopathic Manipulative Therapy

Degenhardt et al. (2007) recruited twenty male subjects: ten with low back pain, ten without. Four osteopathic manipulative therapy (OMT) techniques (articulatory treatment system, muscle energy, soft tissue technique, and Strain-Counterstrain) were performed on areas of subjects' "somatic dysfunction", defined as, "sites of muscle hypertonicity, tenderness, and

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joint restriction" (Degenhardt et al. 2007). Blood was collected prior to (baseline), 30 minutes, and 24 hours after OMT. Increases in β-endorphin and N-palmitoylethanolamide (PEA) – an endogenous analog of arachidonylethanolamide (AEA), or anandamine, an endocannabinoid – were observed 30 minutes post treatment; at 24 hours, similar biomarker changes from baseline were found. Subjects with chronic low back pain experienced greater biomarker alterations following OMT than the control (asymptomatic) group. However, because no true control or sham group was utilized, it is not possible to distinguish whether these changes in biomarkers were due to the placebo effect, or something greater. Although, these data do show that those in pain respond differently to treatment than asymptomatic individuals.

In a blinded, randomized control trial, McPartland et al. (2005) investigated the effects of OMT on plasma endocannabinoid concentrations; that is, AEA and 2-arachidonoylglycerol (2-AG). Thirty-one subjects received either an OMT treatment (biodynamic osteopathy in the cranial field) or a sham treatment. Importantly, subjects were recruited from a patient population of an osteopath who regularly uses OMT; therefore, the patients most likely believe the treatment is efficacious. No changes were observed in 2-AG concentrations in either group. In the sham group, negligible, insignificant changes in AEA were observed (17%). The OMT group experienced a 168% increase (5.02 pmol/mL) in AEA over baseline, but this increase did not achieve statistical significance; however, this difference may certainly be clinically relevant, as indicated by changes in Drug Reaction Scale (DRS) scores. These data suggest that endocannabinoids do play a role in the analgesic effect of OMT.

Spinal Manipulation

A number of studies have investigated the pain modulation mechanisms of spinal manipulation which, as the name implies, is specific only to spinal articulation. The first to do so

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were Vernon et al. (1986), who found a small but statistically significant increase in plasma β-endorphin levels in the experimental group, but not in the sham or control groups. However, two subsequent studies had findings in contrast to Vernon et al. (1986). Christian et al. (1988) and Sanders et al. (1990) both failed to find increases in plasma β-endorphin levels. Christian et al. (1988) did note a decrease in plasma cortisol levels, but this decrease also occurred in the sham groups.

Recently, Plaza-Manzano et al. (2014) compared cervical and thoracic manipulations to a control group. Both cervical and thoracic groups saw decreases in neurotensin, increases in orexin A, and decreases in oxytocin. Only the cervical group saw a decrease in cortisol.

Multiple reviews have also investigated the pain modulating mechanisms of spinal manipulation (Pickar 2002; Vernon 2000), and are in agreement that the analgesic origins are neurophysiological in nature, occurring through some type of descending pain modulation circuit. The exact circuit, however, is not fully understood, and it appears that different types of spinal manipulations, namely the velocity with which and the location at which they are performed, may elicit different neurochemical responses indicative of different descending pain modulation mechanisms.

Knee Joint Manipulation

Skyba et al. (2003) investigated the effects of knee joint manipulation in rats on monoamine, opioid, and gamma-aminobutyric acid (GABA) receptors in the spinal cord. Investigators found that the analgesic effects of knee joint manipulation were not impacted by the spinal blockade of opioid or GABA receptors, but *were* impacted by blocking the receptors of 5-HT and norepinephrine. Therefore, it was posited that descending inhibition following knee

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joint manipulation may be modulated by serotonergic and noradrenergic mechanisms. These findings have yet to be replicated in humans.

Mobilization Therapies

Ankle Joint Mobilization

In mice, ankle mobilization-induced analgesia has been shown to be mediated by EO pathways (Martins et al. 2012). Importantly, researchers noted that the bottleneck in antihypersensitivity was opioid receptor availability, rather than opioid-containing leukocytes. Although opioid receptor availability may be the bottleneck in mice, this is not necessarily true for humans. These data should be replicated in human subjects, and could have large implications for those in chronic pain or those with central sensitization, as these individuals may have decreased opioid receptor availability (DosSantos et al. 2012), and therefore may not benefit as much from this technique.

Mulligan's Mobilization with Movement

Paungmali and colleagues have studied Mulligan's Mobilization with Movement (MWM) in lateral epicondylalgia (Paungmali et al. 2004; Paungmali et al. 2003). Twenty-four subjects with unilateral chronic lateral epicondylalgia were treated with MWM on six occasions at least two days apart. No significant decreases in hypoalgesic effects were seen over the treatment period (Paungmali et al. 2003). In a follow up study, Paungmali et al. (2004) failed to antagonize the hypoalgesic effects of MWM with naloxone, an opioid antagonist, and concluded that MWM works through nonopioid methods. However, as noted by Payson & Holloway (1984), naloxone by itself can produce an analgesic effect due to its inhibitory effects on inflammation and ischemia; therefore, the results of Paungmali et al. (2004) should be called into question.

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Neural Mobilization

Utilizing male Wistar rats and Western blot assays of the PAG, Santos et al. (2014) examined the brains of rats following neural mobilization for mu-, delta-, and kappa-opioid receptor expression. Researchers did not find changes in delta- and mu-opioid receptor expression following neural mobilization, but kappa-opioid receptor expression underwent a significant increase, by 17%. These data indicate that neural mobilization may be modulated by EOs that work on kappa-opioid receptors, such as dynorphin.

Massage Therapies

Massage therapy is often sought for both pleasure and therapy. It has been proposed to work through the gate control theory of pain, initially described by Melzack & Wall (1965) (Field 2014). However, Field (2014) failed to note that different types of massage therapy may work via different mechanisms, nor did Field dive deeply into possible mechanisms. Therefore, a more comprehensive review of massage therapy's mechanisms is warranted.

Connective Tissue Massage

Connective tissue massage is intended to both decrease pain and increase range of motion (Threlkeld 1992). Kaada & Torsteinbo (1989) described a significant increase in plasma β-endorphin levels following connective tissue massage, similar to the time course seen in acupuncture and similar to the magnitude seen during exercise. These results are indicative of a DNIC response, which modulates pain through descending inhibition.

Acupressure

Using naloxone in rats, Trentini et al. (2005) suggested the antinociceptive effects of acupressure are mediated by EOs. Despite this, changes in plasma β-endorphin levels were not observed in follow-up research in humans (Fassoulaki et al. 2007). However, Fassoulaki et al.

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(2007) only investigated the effects of one acupressure point and a sham acupressure point, both on the face. Thus, the effects of acupressure on other parts of the body remain unclear.

Conventional Massage

Regular massage, consisting of effleurage and other common techniques, has been well studied, but its effects are still not completely understood. Day et al. (1987) were the first to note there is no change in plasma β-endorphin or β-lipotropin levels following back massage. Since then, a couple of studies have found that massage increases urine concentration of dopamine and serotonin (Hernandez-Reif et al. 2001; Hernandez-Reif et al. 2004), suggesting that massage therapy's analgesic effects are mediated by dopaminergic and serotonergic pathways, and a review of the mechanisms of massage therapy noted a 31% decrease in cortisol levels and a 28 and 31% increase in serotonin and dopamine levels, respectively (Field et al. 2005). However, a more recent meta-analysis found that not only might the change in cortisol be due to the chance alone, but also its mean effect is unlikely to be clinically significant, as it is only 0.15 standard deviations better than a control (Moyer et al. 2011). Moyer et al. (2011) also addressed numerous methodological issues with prior reviews (such as Field et al. (2005)), which resulted in misleading data and conclusions, as calculated effect sizes were based on within-group (experimental) differences rather than between-group (experimental vs. control).

Future Research

For some therapies, such as manipulation, a minimal amount of force may be required for an analgesic effect (McLean et al. 2002), but whether a minimum force is required for descending inhibition to occur does not seem to be the case, as touch and placebo alone can trigger a descending inhibitory response. However, this may also be treatment-dependent. Being that the gate control theory of pain states that non-noxious stimuli inhibit noxious stimuli, more

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aggressive therapies may be too noxious to trigger a gate control response, but not noxious enough to produce a DNIC response. Thus, more research is needed to shed light on these paradoxical treatment outcomes. Future research should target therapies that have already been shown to be effective, as to prevent the wasting of resources investigating mechanisms that are not clinically meaningful, and should utilize both a control and sham group. Investigators should be cautious when designing experiments that use naloxone, as it can inhibit pain via peripheral mechanisms; thus, it may not be appropriate to use with those who have low back pain (Payson & Holloway 1984). Lastly, it is imperative that researchers be vigilant when interpreting the results of serum levels of EO, as they may not reflect levels seen in the brain or cerebral spinal fluid (Wen et al. 1979).

Conclusion

Nearly all types of manual therapy have been shown to elicit a neurophysiological response that is associated with the descending pain modulation circuit; however, it appears that different types of manual therapy work through different mechanisms. For example, while massage therapy appears to elicit an endogenous opioid response, spinal manipulation does not.

Despite the large popularity and long history of manual therapy, its mechanisms are not truly understood. Understanding its mechanisms may help clinicians choose which therapy is most appropriate for each patient, and may also lead to more effective therapies in the future.

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204 **Table 1.** Findings of studies

Study	Variation	Findings
Degenhardt et al. (2007)	OMT	↑β-Endorphins ↑PEA
McPartland et al. (2005)	OMT	↑AEA
Vernon et al. (1986)	SMT	↑β-Endorphins
Christian et al. (1988)	SMT	→ β-Endorphins
Sanders et al. (1990)	SMT	→ β-Endorphins
Plaza-Manzano et al. (2014)	SMT	↑orexin A ↓ neurotensin ↓ oxytocin
Skyba et al. (2003)	Knee Manipulation	serotonin-mediated norepinephrine-mediated non-GABA-mediated
Martins et al. (2012)	Ankle Joint Mobilization	EO-mediated †
Paungmali et al. (2003)	MWM	No increase in tolerance over treatment period
Paungmali et al. (2004)	MWM	non-EO-mediated †
Santos et al. (2014)	Neural Mobilization	dynorphin-mediated
Kaada & Torsteinbo (1989)	Connective Tissue Massage	↑β-Endorphins
Trentini et al. (2005)	Acupressure	EO-mediated †
Fassoulaki et al. (2007)	Acupressure	→ β-Endorphins
Day et al. (1987)	Conventional Massage	→ β-Endorphins → β-Lipotropins
Hernandez-Reif et al. (2001)	Conventional Massage	↑dopamine ↑serotonin
Hernandez-Reif et al. (2004)	Conventional Massage	↑dopamine ↑serotonin
Field et al. (2005) *	Conventional Massage	↑dopamine ↑serotonin ↓ cortisol
Moyer et al. (2011) ‡	Conventional Massage	→ cortisol

205 * denotes review; ‡ denotes meta-analysis; † denotes a conclusion inferred from naloxone
206 response
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