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The Influence of Cytokines on Altered Pain Thresholds in Obesity

Introduction

Obesity continues to be a dramatic problem throughout the globe. The World Health Organization (WHO) reports that more than 1.5 billion adults worldwide are overweight; of these, over 200 million men and nearly 300 million women meet the criteria for obesity (WHO). In the United States, over 78 million adults and about 12.5 million children and adolescents are obese (Ogden et al. 2010).

The obesity epidemic translates to a significant public health concern since obesity is associated with many pain related co-morbidities including low back pain, diabetic neuropathy, osteoarthritis, headaches, and other musculoskeletal pain conditions (D'arcy 2012). The number of pain issues reported to health care providers is increasing exponentially along with the obesity epidemic since nearly 50% of obese patients regularly experience pain (Kerns et al. 2003). Unfortunately, the association between pain and obesity is not clear. It is well documented that obesity is a pro-inflammatory state and inflammatory markers contribute to the development and modulation of pain; therefore, inflammation may be part of the causation between obesity and pain (Ray et al. 2011). The objective of this translational literature review is to discuss the role of inflammatory markers as modulators of pain in the peripheral and central nervous systems in individuals with obesity.

The Neurophysiology of Pain

Pain is defined as "an unpleasant sensory and emotional experience that is commonly associated with actual or potential tissue damage" (Merskey et al. 1994). In humans, pain is always subjective and is affected by past experiences, context, emotions, cognition, gender, and even cultural and religious influences (Merskey et al. 1994). Acute pain is associated with tissue injury; chronic pain extends beyond normal tissue healing. In the peripheral nervous

system, pain receptors, also called nociceptors, are located in the skin and viscera; nociception is transmitted by A delta and C afferent nerve fibers. Additional nociceptors are located in the muscle and joint; this nociception is transmitted by Group III and IV afferent nerve fibers. Nociceptors are activated via four main stimuli: chemical, mechanical, electrical, and thermal.

After the nocicepter is activated, the pain signal is transmitted along the afferent fiber to the dorsal horn of the spinal cord, specifically lamina I and V-VII. Via the spinothalamic tract, the pain signal crosses to the opposite side of the spinal cord, ascends through the brain stem to the ventroposterior lateral nucleus of the thalamus, and finally to the somatosensory cortex I and II. It is here that the sensory aspect of pain is processed. Another ascending pathway, the spinomesencephalic tract, transmits pain contralaterally from the spinal cord to the midbrain, specifically to the periaqueductal gray matter. Other projections extend from here to the limbic system where the emotional and psychological aspects of pain are processed. In addition to these ascending pathways, there are descending pathways from the cortex that can excite or inhibit pain. Both the peripheral and central nervous system are involved in pain transmission and processing (Kandel et al. 2000).

The Prevalence of Pain in Obese Individuals

Recent research has documented the incidence of pain with obese individuals throughout the lifespan and provided insight into the distinct relation between obesity and pain. Pain prevalence and severity have been linked to obesity in adults, the elderly, and children (Ray et al. 2011; Hitt et al. 2007; Wachholtz et al. 2009; Stone and Broderick 2012). After controlling for demographic and lifestyle variables, obesity is a significant predictor for self-reported pain with an increased incidence of pain at each level of obesity (Hitt et al. 2007). Therefore, there is a dose-response relationship between higher body mass index (BMI) and chronic pain (McCarthy et al. 2009).

Even specific pain conditions such as low back pain, tension-type or migraine headaches, fibromyalgia, abdominal pain, and chronic widespread pain are associated with increased weight in adults (Wright et al. 2010). Similarly, children in the overweight category are more likely to report musculoskeletal pain or discomfort, most commonly in the knee, back or foot (de Sa Pinto et al. 2006; Taylor et al. 2006; Stovitz et al. 2008) and headaches (Bell et al. 2007; Hershey et al. 2009). In addition, the impact of pain on functional status and health-related quality of life is more significant in individuals with higher BMI compared to normal BMI (Marcus 2004). The co-occurrence of pain and obesity have an additive negative effect on health-related quality of life as evidenced in patients seeking treatment for obesity and for chronic pain (Marcus 2004; Barofsky et al. 1997; Janke et al. 2007). Consequently, obese individuals are at high risk in developing chronic pain, which negatively impacts their quality of life to a greater degree than obesity alone (Marcus 2004). The presence of pain in obesity can also decrease participation in physical activities and this can lead to additional weight gain (Taylor et al. 2006). Clinical pain is highly evident in individuals with obesity and can influence their quality of life, lead to chronic pain, and contribute to a sedentary lifestyle which further increases obesity.

Experimental Pain and Obesity

Since the 1980s, researchers have been examining specific aspects of pain in individuals with obesity. This research can be difficult to evaluate since researchers have examined pain thresholds, pain sensitivity, and pain tolerance. Pain thresholds are defined as the minimum amount of stimuli required to produce a report of pain in an individual. Pain sensitivity is related to a subject's pain threshold level; an elevated pain threshold demonstrates that pain sensitivity has decreased. Pain tolerance is the maximum stimulus that a subject can endure. It can be difficult to summarize results from the variety of studies due to methods. Furthermore, there are conflicting results in experimental pain as to whether obesity in animals or adults contributes to higher or lower pain thresholds and tolerance (Table 1).

It is crucial to understand the difference between pain and nociception when comparing human and animal research. In humans, pain includes both the sensory and emotional aspects to a noxious stimulus. However, in animal research, pain must be classified as "nociception" because it does not include the emotional aspect and is inferred from the animal's behavioral response to a noxious stimulus.

Animal research supports increased and decreased nociception associated with obesity. Obese rats demonstrated attenuated nociception (a higher thermal threshold) by increased tail flick latency to a thermal stimulus compared to normal weight controls (Ramzan et al. 1993). In rabbits, obesity decreased the amount of time spent in pain behavioral responses in response to a 1st phase formalin test to the hind limb paw; this demonstrated an increased thermal threshold (Sinha et al. 2009). In contrast, Zucker rats (a genetic model for research on obesity and hypertension) exhibited shorter latencies to nociceptive mechanical stimuli in tail-flick and tail-pinch methods than normal weighted ones (Roane and Porter 1986). There is minimal animal research in this area and it shows differences in nociception in response to experimental pain. In the animal model, nociception seems to be dependent on the stimulus, thermal versus mechanical.

Human research also shows conflicting results with experimental pain associated with obesity. Research has shown that obesity is linked with higher pain thresholds (Khimich 1997; Maffiuletti et al. 2011; Raymond et al. 1995; Zahorska-Markiewicz et al. 1983; Zahorska-Markiewicz et al. 1988). Pain thresholds to an electrical stimulus on the forearm and arm were observed to be higher in obese subjects over normal lean subjects; obese individuals appear to be less susceptible to pain with the correlation existing between overweight and the pain threshold (Zahorska-Markiewicz et al. 1983). Additional work by Zahorska-Markiewicz in 1988 demonstrated that sensory and pain thresholds to an electrical stimulus on the forearm were higher in obese versus lean controls (Zahorska-Markiewicz et al. 1988). Pain detection

thresholds in response to a mechanical stimulus on the fingers were elevated in obese subjects when compared to controls with no significant differences in pain tolerance levels between the groups (Raymond et al. 1995). Higher pain thresholds to a mechanical stimulus on the forearm were also evident in subjects with excessive body weight in comparison to normal body weight controls indicating that they felt less pain (Khimich 1997).

Not all human research with experimental pain shows increased pain thresholds and tolerance. In contrast, a lower sural nerve nociceptive-flexion reflex was demonstrated in obese women showing a significant reverse correlation between degree of overweight and the threshold of the nociceptive reflex (Pradalier et al. 1981). In obese subjects, pain sensitivity was increased as demonstrated by obese individuals displaying decreased mechanical pain thresholds assessed by a constant force applied to the finger (McKendall and Haier 1983).

Significant differences in pain responses in obese animals and humans have been demonstrated in the previous research studies. There is noteworthy variability with the type of stimulus (mechanical, electrical, thermal) and the body location to which it was applied. Also, it is important to remember that experimental pain is not the same as clinical pain. The clinical reports of pain in obesity are very strong, but experimental pain is more variable. This suggests that in response to a noxious stimulus, obesity may or may not attenuate pain thresholds and tolerance.

The Chronic Inflammatory State of Obesity

In order to understand the linking of pain and obesity through the mechanism of inflammatory markers, it is essential to know the substantial role that inflammatory markers play in obesity. Obesity is not just an imbalance of energy intake and expenditure. Adipose tissue is no longer considered a passive energy store but rather a major endocrine organ (Berggren et al. 2005; Ferris and Crowther 2011). Increased adiposity is linked to increased macrophage accumulation

and ultimately an increase in pro-inflammatory marker production which acts on a variety of physiological processes throughout the body (Weisberg et al. 2003). Specifically, inflammatory markers are secreted by adipose tissue and can create a persistent low-grade inflammatory state in obese individuals. These biologically active molecules are called cytokines or adipokines when they originate in adipose tissue. Cytokines are proteins and peptides that are secreted by cells which then act as cell messengers, including pro-inflammatory mediators. Cytokines can influence insulin sensitivity, glucose metabolism, inflammation and atherosclerosis (Cancello et al. 2006). Therefore, adipose tissue plays an important role in the complex cross-talk between organs regulating the body's homeostasis (Fischer-Posovszky et al. 2007).

The most commonly studied inflammatory markers associated with obesity are tumor necrosis factor α (TNFα) and interleukin-6 (IL-6). In obesity, these inflammatory markers are linked with physiological mechanisms that lead to compromised health. TNFα, for example, can stimulate the production of atherosclerotic lesions leading to endothelial dysfunction and hypertension (Arslan et al. 2010; Lyon et al. 2003); furthermore TNFα impairs insulin signaling which negatively affects glucose transport (Keller et al. 2004; Umpaichitra 2006). IL-6 has been shown to negatively impact insulin sensitivity and endothelium functioning (Arslan et al. 2010). Il-6 has been shown to inhibit TNFα production and increase the number of voltage-dependent sodium channels (Aderka et al. 1989; Satoh et al. 1988). The resultant inflammatory state, as demonstrated by elevated levels of TNFα and IL-6 in obese individuals, contributes to impaired metabolic and cardiovascular health associated with obesity (Wisse 2004).

The Effects of Cytokines on the Nervous System

In tissue injury, the initial role of cytokines is to sustain or reestablish homeostasis; however, sustained or excessive cytokine production can lead to damage (Rothwell and Hopkins 1995). Literature has shown that cytokines can negatively influence the function of neuronal cells

(Benveniste 1992). Also, the nervous system can both respond to cytokines and produce them (Hopkins and Rothwell 1995). Obese individuals with a chronic inflammatory state due to altered cytokine production may have different pain perception. For example, in obese individuals, elevated levels of TNFα and IL-6 are involved in the modulation of nociceptive pathways in both the peripheral and central nervous systems (Sommer 2001; Oka et al. 1993; Ferreira et al. 1993; Bianchi et al. 1992). It is important to distinguish the potential mechanisms on these peripheral and central nervous system components to alter pain in obesity (Table 2).

Cytokines and the Peripheral Nervous System

Cytokines, associated with obesity, offer the potential to affect the peripheral nervous system, specifically the afferent nociceptor. Changes in the environment from cytokine levels can influence sensory neurons to develop alterations which lead to modification of the transduction, conduction, and transmission functionality of these neurons (Cunha et al. 1992; Woolf and Costigan 1999). Sensitization of the pain receptor causes hyperalgesia and can be related to the inflammatory environment from dose-dependent levels of TNFα and IL-6 (Cunha et al. 1992).

With tissue injury, silent nociceptors are inactive under normal conditions but are activated by inflammation and can then respond to noxious or non-noxious (innocuous) mechanical stimuli (Kandel et al. 2000). Silent nociceptors were initially discovered in response to injection of Kaolin, a clay substance used to mimic clinical pain (Schaible and Schmidt 1985; Schaible and Schmidt 1988). No research to date has assessed the role of cytokines in activating silent nociceptors, but it is hypothesized that cytokines may be part of the inflammatory impact in activating these silent nociceptors and creating pain associated with obesity.

Another response to inflammation is peripheral sensitization, an increased responsiveness of peripheral afferent nociceptors after tissue injury. It affects the ability of the peripheral nervous

system to send information to the central nervous system. Peripheral sensitization is characterized by an increased firing rate of the nociceptor, decreased threshold for firing of the nociceptor, and increased release of excitatory neurochemicals such as substance P, aspartate, glutamate, and calcitonin gene related peptide (Sluka and International Association for the Study of Pain 2009). With peripheral sensitization, a larger pain signal is delivered to the spinal cord resulting in hyperalgesia.

Aspects of peripheral sensitization are highlighted in the research work related to TNFα. An animal study showed that intraplantar (peripheral) injections of TNFα reduced mechanical nociceptive thresholds and induced mechanical allodynia (a noxious response to an innocuous stimulus) and thermal hyperalgesia in rats (Cunha et al. 1992). Through injection of TNFα on individual C nociceptors of the sural nerve of rats, it was demonstrated that TNFα sensitized C nociceptors (Junger and Sorkin 2000). TNFα injections into corresponding receptive fields also created transient bursting or more sustained and persistent C nociceptor activity (Junger and Sorkin 2000). The main components of peripheral sensitization may be occurring in response to peripheral exposure of TNFα.

Another obesity cytokine, IL-6 is associated with increased pain and hyperalgesia (Sommer 2001). IL-6 is suggested to significantly change the survival, histological behavior, and the functionality of cells related to nociception or pathologic pain (De Jongh et al. 2003). For example, IL-6 signaling starts an intracellular cascade system that shares intracellular signal proteins resulting in stronger nociception (De Jongh et al. 2003). Intraplantar injections of IL-6 have produced hyperalgesia or allodynia in rats (De Jongh et al. 2003). Similarly, intramuscular IL-6 injections into mice resulted in long lasting mechanical hyperalgesia (Manjavachi et al. 2010). IL-6 has been shown to be a major element of the nociceptor environment that contributes to nociceptor sensitization and heat hyperalgesia (Obreja et al.

2002). Obese individuals, who display elevations in IL-6, have evidence for a cytokine mechanism related to increased peripheral sensitization.

In contrast, animal research also lends support for TNFα to alter pain via damage to the peripheral nerve itself. TNFα is known to directly cause demyelination and axonal degeneration in rats (Stoll et al. 1993). A delta nociceptors are myelinated and transmit the "first pain", while C nociceptors are unmyelinated and transmit the "second pain" (Kandel et al. 2000). However, if afferent fibers are demyelinated or potentially have axonal degeneration from increased exposure to TNFα, the first pain would be slower in transmission or unable to be transmitted to the spinal cord. This would result in decreased pain as a result from elevated TNFα exposure from obesity. While this is not demonstrated in the clinical pain associated with obesity, this may explain some of the experimental pain research results.

Another peripheral aspect that cytokines may affect is prostaglandins which are one of the most important mediators of inflammatory tissue injury hyperalgesia. Prostaglandin synthesis, which is stimulated by a number of cytokines including TNFα and IL-6, is a major feature of both acute and chronic inflammatory states (Rothwell and Hopkins 1995). This increase in prostaglandins sensitizes sensory neurons, decrease their activation threshold, and enhance their responses to other stimuli (Dray 1995). TNFα promotes eicosanoid synthesis through stimulation of increased transcription of synthetic enzymes (Rothwell and Hopkins 1995). IL-6 participates in increased pain response (hyperalgesia) in response to TNFα through prostaglandins (Rothwell 1991; Dinarello et al. 1991). Pro-inflammatory cytokines, such as TNFα and IL-6, increase prostaglandin synthesis. Therefore, there is a synergistic effect of hyperalgesia in obesity through several peripheral mechanisms.

Cytokines and the Central Nervous System

Increasing evidence suggests that pro-inflammatory cytokines enhance pain via central mechanisms in both the spinal cord and brain. Chronic pain conditions induce pro-inflammatory cytokines in the spinal cord; intrathecal injections of these cytokines enhance pain; and spinal blockade of cytokines attenuates chronic pain (Kawasaki et al. 2008). In addition, cytokines may influence the central nervous system aspect of pain both directly and indirectly (Szelenyi 2001). Unfortunately, less is known how these inflammatory cytokines specifically alter synaptic transmission and neuronal activity in the central nervous system.

Central sensitization is an increased excitability of the nociceptive neurons in the central nervous system to their normal afferent input. The five main characteristics of central sensitization include: 1) increased receptive field size, 2) increased response to a noxious stimulus (hyperalgesia), 3) increased response to a non-noxious stimulus (allodynia), 4) increased spontaneous firing, and 5) decreased activation threshold (Sluka and International Association for the Study of Pain 2009). Pro-inflammatory cytokines, such as TNFα and IL-6, enhance pain via central mechanisms to accelerate central sensitization in rats (Kawasaki et al. 2008). Specific to animals, intracerebroventricular or intrathecal injections of IL-6 have produced hyperalgesia or allodynia in rats (De Jongh et al. 2003). Due to elevated inflammatory markers secreted from adipose tissue, central sensitization may explain the increased pain associated with increased BMI.

A pivotal study investigating the cytokine mechanisms of central sensitization was completed by Kawasaki et al. in 2008. Kawasaki stated that "central sensitization is caused by increased excitatory synaptic transmission and decreased inhibitory synaptic transmission". Past research had shown that most neurons in lamina II (part of the spinothalamic tract) of transverse spinal cord slices are excitatory and pro-nociceptive (Baba et al. 2003; Kohno et al. 2005; Moore et al. 2002; Yang et al. 1998). Through patch-clamp recordings in lamina II neurons of isolated spinal

cord slices of Sprague Dawley rats, the effects of TNFα and IL-6 on excitatory and inhibitory synaptic transmission were compared (Kawasaki et al. 2008). TNFα heightened the frequency of spontaneous excitatory postsynaptic current (EPSCs) to induce glutamate (an excitatory neurotransmitter) release from central terminals of primary afferents (Kawasaki et al. 2008; Baba et al. 2003). In contrast, IL-6 decreased the frequency and amplitude of inhibitory postsynaptic currents (IPSCs) and suppressed inhibitory neurotransmission through suppression of GABA and glycine (inhibitory neurotransmitters) induced currents (Kawasaki et al. 2008). In the superficial dorsal horn neurons of the spinal cord, the synaptic mechanisms of TNFα and IL-6 are individual but also corresponding through their actions of increasing excitatory synaptic transmission (TNFα) or decreasing inhibitory synaptic transmission (IL-6) to create central sensitization (Kawasaki et al. 2008) . Therefore, pro-inflammatory cytokines evident in the inflammatory state of obesity can induce central sensitization.

In other experiments, injection of TNFα and IL-6 into spinal cord cerebral spinal fluid has created marked heat hyperalgesia (Kawasaki et al. 2008). The overall effect of TNFα and IL-6 are both pro-nociceptive, but specifically intrathecal IL-6 (a simulation of the effects of obesity) has produced allodynia in otherwise normal rats (DeLeo and Yezierski 2001). These central injections simulate the increased pro-inflammatory cytokines evident in obesity to help explain heat hyperalgesia and allodynia.

A final central nervous system component that is potentially affected by the chronic inflammatory state associated with obesity is the hypothalamus and hippocampus. Pain by definition is a both a sensory and emotional response; the central nervous system allows nociception to be transmitted to critical processing areas in the brain for these sensory discriminative (somatosensory cortex I and II) and motivational affective components (anterior cingulate and anterior insular cortex). These motivational-affective processing areas are intimately connected to the limbic system which contains the hypothalamus, known to regulate

the pain response, and the hippocampus, which plays a strong role in our emotional life and converts short-term memory to long-term memory (The Limbic System [Online]). Brain research shows that the highest density of cytokine receptors are located in the hypothalamus and hippocampus, areas noted to be critical in pain processing (Hopkins and Rothwell 1995). If peripheral cytokines from adipose tissue are able to reach these central areas, they could be influencing pain regulation and pain memory formation. Additional research in this area is required to make more concrete statements about the potential role of peripheral cytokines from adipose tissue crossing the blood brain barrier and affecting central receptors in the hypothalamus and hippocampus.

Cytokines and the Opioid System—A Peripheral & Central Effect

Opioid receptors are located throughout both the peripheral and central nervous system. After tissue injury, opioid receptors are upregulated to reduce pain in inflamed tissues (Kandel et al. 2000). The opioid system is also affected by cytokines. IL-6 knockout mice demonstrate fewer opioid receptors in the midbrain, larger hypothalamic levels of β-endorphin, and decreased analgesic response to morphine; therefore, IL-6 may be playing a role in the responses to nociceptive stimuli and modulating the opioid pathway (Bianchi et al. 1992). It has also been demonstrated that morphine is less potent in obese versus lean rats suggesting a defect in the endogenous opioid systems of obese Zucker rats (Roane and Porter 1986). Increased opioid receptors have been found in obese animal models of obesity (Cozzolino et al. 1996; Smith et al. 2002); a possible link between obesity and the opioid receptors density could be cytokines associated with obesity. In addition, increases in endogenous opioid levels have been reported in obese humans (Cozzolino et al. 1996; Givens et al. 1980; Karayiannakis et al. 1998). Another reason for the variability of results in the experimental pain studies may be the influence of cytokines on the opioid receptor representation and opioid levels in obese individuals leading to decreases in pain.

The changes to the opioid system from cytokines may be indirect as ghrelin may be the mediator. Ghrelin is a hormone related to obesity that affects hunger; obese individuals have decreased levels while lean individuals have increased levels. Ghrelin receptors have been shown to be expressed in various brain areas that influence the transmission of noxious messages such as the brainstem and hypothalamus (Kojima and Kangawa 2005; Zigman et al. 2006). Both intracerebroventricular, intraperitoneal, and intraplantar ghrelin have been shown to effectively counteract the development of hyperalgesia induced by intraplantar carrageenan (a seaweed derivative to induce inflammation) in rats (Sibilia et al. 2006). Therefore, ghrelin acts as an inhibitor on inflammatory pain through an interaction with the central opioid system (Sibilia et al. 2006). In obese individuals, ghrelin is decreased resulting in less inhibition. Whether administered centrally or peripherally, ghrelin exerts an inhibitory role on the development of inflammation and hyperalgesia (Sibilia et al. 2006). This inhibitory role evolves from ghrelin inhibiting the expression of pro-inflammatory cytokines such as TNFα and IL-6 (Dixit et al. 2004). These cytokines contribute to both central and peripheral inflammatory pain hypersensitivity (Samad et al. 2001). With the decrease in ghrelin in obese individuals, IL-6 and TNFα remain elevated and may be even higher in obese individuals due to additional production by adipose tissue; this would increase pain.

Conclusion

The obesity epidemic has created a significant public health concern with the majority of obese individuals reporting clinical pain. Obesity and clinical pain have an established connection in literature across the lifespan, but consensus over the true definition of altered experimental pain in obesity is not set. Obese individuals demonstrate elevated levels of cytokines, such as TNFα and IL-6, which can create a chronic inflammatory state leading to impaired health (Figure 1). These inflammatory markers associated with obesity are also related to pain signaling and transmission in both the peripheral and central nervous systems. Therefore, cytokines may be

altering the neurophysiological properties of peripheral nociceptors and central neurons via quantitative changes in inflammation involved in nociception. Peripheral and central sensitization may be enhanced by cytokines. In addition, prostaglandins and the opioid systems may be influences by cytokines. Not all pain research involving cytokines supports the increased report of clinical pain in obesity, but this conflict may expound the variability in research results involving experimental pain.

Future Research

These conflicts in research in both animal models and humans provide numerous avenues for additional research in the study of obesity-associated pain. Future research involving assessment of obesity variables (BMI and measures of body composition), peripheral and central cytokine levels, and pain thresholds/tolerance levels are needed to see the direct and indirect mechanisms of cytokines on pain in the peripheral and central nervous system. A large amount of the research has been completed in animal models where aspects of emotion and social influence are not as strong as in humans. Additional research is necessary in humans to establish the association of pain reports in individuals with obesity and the inflammatory state created by cytokines from obesity. Obesity interventions, such as physical activity and exercise, promote changes in body composition through decreases in fat mass. This change in fat mass may decrease the inflammatory state brought on by adipose tissue. Ultimately, exercise may decrease pain because less pro-inflammatory cytokines are enhancing peripheral and central sensitization. In addition, exercise may also promote an anti-inflammatory state and decrease pain through exercise induced hypoalgesia. Adults and pediatric studies are need in this area to determine how exercise influences changes in cytokine expression on pain in obesity during acute and long term exercise training.

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Table 1: Is Experimental Pain Altered in Obesity?

Author	Year	Animal Study	Human Study	Pain or Noc ↑	Pain or Noc ↓	No Change	Results
Khimich	1997		✓		✓		Higher pain thresholds to mechanical stimulus on the forearm in subjects with excessive body weight compared to normal weight controls.
McKendall & Haier	1983		✓	✓			Decreased mechanical pain thresholds in obese individuals.
Pradalier et al.	1981		✓	✓			Lower sural nerve nociceptive-flexion reflex in obese women.
Ramzan et al.	1993	✓			✓		Increased thermal pain threshold as observed by increased tail flick latency in obese animals.
Raymond et al.	1995		✓		✓	✓	Elevated pain detection thresholds to mechanical stimulus on fingers in obese compared to controls. No significant differences in pain tolerance thresholds between the groups.
Roane & Porter	1986	✓		✓			Decreased latency to nociceptive mechanical stimuli by Zucker (obese) rats than normal weight rats.
Sinha et al.	2009	✓			✓		Increased thermal threshold by decreased time in pain behaviors in response to formalin test with obese rabbits.
Zahorska-Markiewicz	1983		✓		✓		Elevated pain thresholds in obese subjects over normal lean controls in response to electrical stimulus on forearm and arm.
Zahorska-Markiewicz	1988		✓		✓		Sensory and pain thresholds were higher in obese versus lean controls from electrical stimulus on forearm.

Table 2: Are TNFα or IL-6 a Possible Mechanism that Alters Nociception/Pain in the PNS or CNS?

Author	Year	Animal Study	Human Study	TNFα	IL-6	CNS Effect	PNS Effect	Notes
Baba H et al.	2003	✓		✓		✓		Central Sensitization
Bianchi M et al.	1992	✓			✓	✓		Opioid system
Cunha, FQ et al.	1992	✓		✓			✓	Peripheral Sensitization
De Jongh RF et al.	2003	✓			✓	✓	✓	Central & Peripheral Sensitization
DeLeo JA & Yezierski RP	2001	✓		✓	✓	✓		Central Sensitization
Dinarello CA et al.	1991	✓			✓		✓	Prostoglandins role
Dixit VD et al.	2004		✓	✓	✓	✓		Ghrelin as mediator
Ferreira SH et al	1993	✓		✓	✓	✓	✓	Central & Peripheral Sensitization
Junger H & Sorkin LS	2000	✓		✓			✓	Peripheral Sensitization
Kawasaki Y et al.	2008	✓		✓	✓	✓		Central Sensitization
Manjavachi MN et al.	2010	✓			✓		✓	Peripheral Sensitization
Obreja O et al.	2002	✓			✓		✓	Peripheral Sensitization
Samad TA et al.	2001	✓		✓	✓	✓	✓	Ghrelin as mediator
Stoll G et al.	1993	✓		✓			✓	Demyelination & Axonal Degeneration

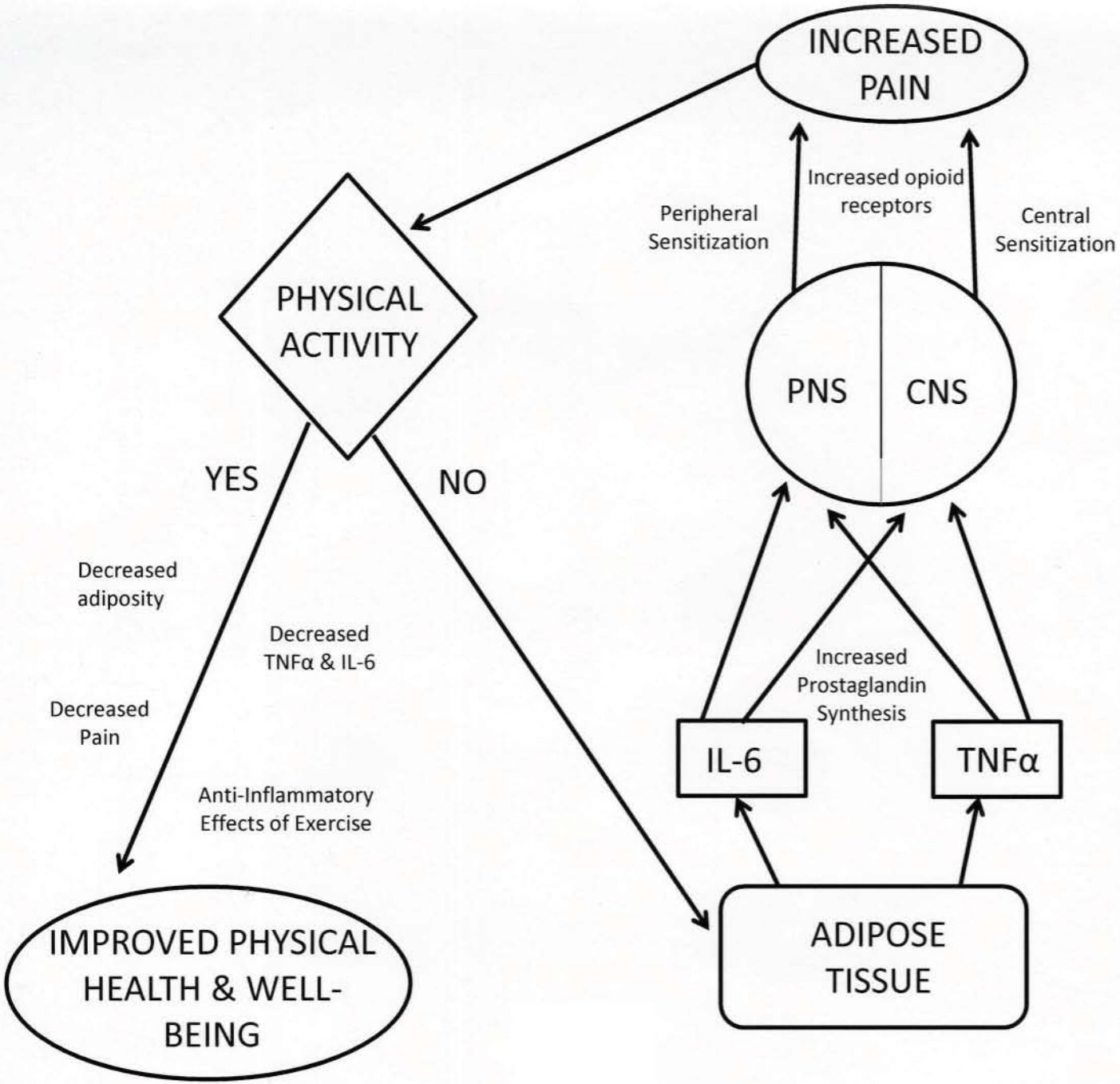

Figure 1: **The Influence of Cytokines in Obesity-Associated Pain**. Adipose tissue produces the cytokines TNFα and IL-6. These cytokines affect the peripheral and central nervous systems to increase pain associated with obesity through peripheral and central sensitization. TNFα and IL-6 also increased prostaglandin synthesis which increases pain. Ghrelin may be a mediator between the link of cytokines and the opioid system to increase pain in obese individuals. Physical activity is a critical intervention to decrease adiposity, inflammatory markers, and pain to improve physical health and well-being.