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BLOOD PRESSURE MEDIATED PAIN MODULATION

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Abstract- Several different perspectives concerning the origins of blood pressure-related hypoalgesia have been reported over the last few decades but the mechanisms to unfold the relationship between variable pain perceptions amongst individuals still remains unclear. This article is critical review of existing observations of scientific reports on blood pressure mediated pain modulation and suggests a conceptual central mechanism to explain hypoalgesia associated with elevated resting BP in individuals.
Key words- Hypoalgesia, Blood pressure, Electro-acupuncture stimulation, Pain tolerance

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Introduction

It is a well established and known fact that acute pain causes a generalized arousal response accompanied by a rise in blood pressure along with sensory perception however, it is not clear why the magnitude of the pain perception differs from individual to individual and its relevance with basal blood pressure. Several studies have reported an association of hypertension with reduced pain sensitivity, though the precise mechanism of headache due to hypertension is unclear. Association of heightened sympathetic tone and reduced pain sensitivity in battle field or sports field is an age old observation. Growing Evidences over the last three decades have demonstrated that hypertensive subjects demonstrate decreased pain sensitivity. These observations are drawn mainly from experimental studies, though a few human studies have also been reported. Data from these studies demonstrate that increased pain tolerance is associated in humans with a parental history of hypertension, exaggerated cardiovascular reactivity, and elevated blood pressure [1-3]. There are very few epidemiological studies on blood pressure related pain other than headache, on the other hand most studies report that hypertensive patients experience less intense pain during angina and myocardial infarction then the normotensive patients. Another survey based report reveals that lower prevalence of headache has been observed in individuals with higher systolic BP (> 150 mmHg) as compared to those with BP ≤140. Increased pulse pressure has also been related to a low prevalence of headache in both the sex [4-5].

Individual variability in magnitude of pain tolerance was a consistent finding of experimental studies conducted during the year 1984-1990 and it was proposed that variability in basal blood pressure might be one of the factors amongst other psycho-physical factors that would have influenced the magnitude of behavioral responses evoked by nociceptive and anti-nociceptive manipulations both in animal as well as human studies (6-10). Thus the relationship between magnitude of pain tolerance and blood pressure seems more complex and remains unclear as this relationship appears to be influenced by multiple factors such as type of pain syndrome, duration of pain, magnitude of blood pressure changes, pain sensitivity and responses to pain. Most of the experimental studies showed a correlation of pain and its relief with alteration in blood pressure and further more, the magnitude of this effect was found some times related to the background blood pressure of the individual. This later relationship needs in depth exploration. This article aim to review the existing observations on altered pain tolerance mediated by variations in arterial blood pressure to understand whether basal blood pressure level affects pain sensitivity and if so what are the mechanisms and its significance?

Electro-Acupuncture like Stimulation (EAS) and Analgesia

In anaesthetized cats effect of electro-acupuncture like stimulation (EAS) on sciatic nerve stimulation evoked changes in blood pressure was studied. Sciatic nerve stimulation produced either a pressor or a depressor effect on BP depending on intensity of stimulation. The magnitude of pressor and depressor effects varied from animal to animal and one factor contributing to this variability seemed to be the basal BP. Higher basal BP was associated with a smaller pressor and marked depressor effect. Considering that pressor effect is linked to stimulation of Aδ fibers involved in acute pain and depressor effect evoked by C fibers involved in chronic pain it seemed that animals with higher basal BP had decreased responsiveness to acute pain and enhanced responsiveness to chronic pain. Part of this assumption i.e association of decreased pain sensitivity with higher basal BP gets confirmed and reconfirmed by a number of recent studies conducted on various rat models of hypertension [11]. Comparison of pressor or depressor

effects before and after electro-acupuncture stimulation (EAS) revealed that varying degree of potentiation in depressor and attenuation of pressor response accompanied by slight fall in basal BP after EAS. It was inferred that electro-acupuncture causes parasympathetic activation and sympathetic suppression. The magnitude of change seemed to be determined by basal BP level or the basal autonomic tone. Animals having lower basal BP demonstrated lesser depressor effect with sciatic nerve stimulation and also lesser EAS induced potentiation of depressor effect. These finding suggest that reduced sympathetic discharge and increased vagal tone are the contributory factors for acupuncture stimulation induced analgesia [8-9]. A patient to patient variability in degree of pain relief with electro acupuncture has also been reported. Patients with acute painful conditions like frozen shoulder, post herpetic neuralgia reported pain relief following EAS. It is therefore hypothesized that analytical study of the EAS with simultaneous recording of basal BP vis -a- vis measurement of pain tolerance amongst the patients with acute painful conditions associated with increased BP may explain the individual variability in effectiveness of electro acupuncture. In one group of pain patients undergoing acupuncture therapy limb blood flow was recorded before and after acupuncture. In more than 70% patients an increase in blood flow was observed following acupuncture, however the degree of analgesia varied from patient to patient and so was variation in blood flow changes. Effectiveness of electro-acupuncture seemed correlated to attenuation of sympathetic tone as evidenced by improved limb blood flow and some fall in blood pressure following EAS. Comparison of autonomic status of herpes zoster and post herpetic neuralgia patients revealed an elevated sympathetic tone in post herpetic neuralgia cases as compared to that in herpes zoster patients.

Pain Sensitivity and Blood Pressure

Increased pain threshold (decreased pain sensitivity) associated with increased parasympathetic tone was observed in female adolescent patients of anorexia nervosa [13]. Makulska, et al [14] have observed a strong correlation between drop in blood pressure and increase in pain threshold (decreased pain sensitivity) after intracerebroventricular endorphin-2 both in spontaneously hypertensive and normotensive rats. This kind of association of analgesia with a fall in BP was observed by us in the experiments in which a gradual fall in basal blood pressure was seen as a result of low frequency low voltage electro acupuncture stimulation in animals [15].

Altered blood pressure following administration of pain relieving drugs suggests close interaction between brain regions controlling blood pressure and pain perception. Hypertension in patients can cause hypoalgesia [16]. Ghione S., et al. [17] have reported a strong association between hypertension and hypoalgesia as tested with a commercial tooth pulp tester in a large series of subjects with borderline or established hypertension and in three groups of normotensive controls. Luigina Guasti, et al [18] observed correlation between 24 hour blood pressure trend and pain sensitivity and reported that higher pain threshold and tolerance in hypertensive group attributed to sustained levels of arterial BP. William Maixner, et al [19] have also observed higher pain threshold and pain tolerance in subjects having high resting blood pressure. Viggiano A., et al [20] report higher pain threshold in hypertensive patients as compared with the normotensive subjects. Cambell and Ditto [21] have reported reduced pain perception in hypertensives and normotensives at the risk of developing hypertension and this they have suggested to be due to increased endogenous opioids release or receptor sensitivity. Our studies on Angora rabbits showed that obesity attenuated formalin induced pain sensitivity [22]. Obesity is invariably associated with raised blood pressure it does imply an association of reduced pain sensitivity with high BP. This reduced pain sensitivity may be due to elevated opiate activity which is reported in obese rodents. But this kind of relationship between obesity and raised endorphin activity was not seen in obese human subjects [23]. Koltyn et. al [24-25] reported that hypoalgesia following good workout could be due to increase in blood pressure and endogenous opioids released during exercise which is widely accepted and well supported in human research.

There are some reports that show no correlation between pain sensitivity and blood pressure: Guasti, et al has reported no relationship between blood pressure changes and pain sensitivity during altered thyroid status [26]. Maixner, et al. found no relationship between blood pressure and sensitivity to acute pain in patients with temporomandibular joint disorders[27].In a sample of healthy normotensive women significant elevation of BP was seen following isometric exercises but these were not associated with alteration in pain perception[28]. Further acute pain is generally accompanied by an elevation of blood pressure and most of the pain relieving measures (EAS, TENS, some of the analgesics) bring about a slight fall in blood pressure. In most of our studies, analgesia was not accompanied by increase in blood pressure rather the analgesic manipulations like electro acupuncture invariably produced a slight fall in the blood pressure. Cambell and Ditto, have reported a similar observation of significant reduction in systolic blood pressure following low frequency transcutaneous nerve stimulation [29]. Maixner et.al demonstrated in his elevated resting BP subgroup was associated with higher pain threshold and tolerance as compared to the normotensive control group. However, in patients with temporomandibular disorders (TMD) resting BP did not have this influence on the pain sensitivity. The study concluded that resting BP influences thermal and ischemic pain perception in pain free women but not women with painful TMD and this may be due to impaired pain regulatory system in TMD [27].

Bruehl, et al. revealed a weak inverse correlation between symptoms of pain and BP in patients with duration of pain less than one year and a positive correlation in those with more than 2 year duration [30] while patients with frequent intense chronic pain showed higher BP levels. Basal BP of patients with chronic pain varied with the cause of pain. Patients suffering from musculo-skeletal pain or fibromyalgesia or migraine demonstrate a higher basal BP. Patients with malignancies associated pain generally has their basal BP at a lower level. So it is suggested that normal pain free individuals with higher resting BP are likely to have higher pain threshold i.e. lower pain sensitivity as compared to those with lower resting BP.

Though there is no single mechanism to explain the correlation of BP and pain sensitivity is possible as yet, some hypothetic possibilities are given below.

a. Reduced pain sensitivity in normal individuals with higher resting blood pressure may be due to cardiovascular effects on the central pain regulating system. Absence of this effect in patients with painful temporomandibular disorders could indicate

impairment of central neural pain inhibitory mechanisms.

b. Bradley K. Taylor et.al have done extensive studies in evaluating contribution of several brain regions (amygdale, locus coeruleus, and rostral medulla) in pain signaling According to their studies it is suggested that nociceptive processing is altered in individuals with inherited hypertension. Their animal studies point to brain stem noradrenergic neurons in locus coeruleus which are implicated both nociceptive transmission and also hypertension. A direct evidence to show that central pain regulating mechanisms is affected by blood pressure or cardiovascular responses needs further exploration. Interaction between pain mechanisms and cardiovascular reflexes is also indicated in the report that baroreflex sensitivity is altered in chronic low back pain subjects.
c. Involvement of endogenous opioids (endorphins) as mechanisms underlying hypoalgesia associated with hypertension has been suggested in several research papers [23-25]. This hypothesis assumes an increased level of endogenous opioids in individuals with higher BP but needs further experimental confirmation. Also on the contrary endorphins & morphine administration induced analgesia is accompanied by a fall in blood pressure. Intravenous morphine administration produces a fall in BP [6]. Hypoalgesia following a good work out has been suggested to be due to increase in blood pressure and endogenous opioids released during exercise. This hypothesis is well supported in human research, and it has been verified that it plays a significant role. So there seems simultaneous existence of hypertension, hypoalgesia and increased levels of endorphins under certain situations.
d. Recently the conceptually regulatory collection of brain regions "pain matrix," which broadly include the rostral anterior cingulate cortex (rACC), the pregenual cingulate cortex (pCC), somatosensory cortex 1 and 2, the insula, amygdala, thalamus, and the PAG has been proposed as a central mechanism to explain pain modulation and relationship of pain modulation with various psychosocial as well as psycho-physiological conditions. It is suggested that the areas of pain matrix demonstrate overlap among brain sites activated by opioids and are involved in cognition, emotion, motivation, and sensation as well as pain perception functions. These regions, acting together in the context of modulation of nociception, appear to give rise to the experience of pain. It is noted that analgesic drugs as well as expectation, distraction, emotional context, and other factors engage several nodes of the pain matrix to change the pain experience [31].

Significance

A clear understanding of relationship between pain sensitivity and blood pressure status is likely to help in judicious management of pain particularly in analgesic requirement of normotensive, hypotensive and hypertensive patients.

Conclusions

Acute painful situation causes a rise in blood pressure**.** A slight fall in blood pressure accompanies relief of acute pain. Electro-acupuncture seen to be more effective in acute painful conditions. Pain relieving manipulations like electro-acupuncture, morphine produce some drop in basal BP. A higher pain threshold (decrease in pain sensitivity) is seen in normal / pain free individuals having higher resting BP. This seems to be due to connections of pain matrix linking the PAG to the amygdala and cortical sites suggest that interactions between the prefrontal cortex and the amygdala provide emotional-affective modulation of cognitive functions in pain. The amygdala plays important roles in emotional responses, stress, and anxiety and is believed to be a critical component of the pain matrix. This region may contribute significantly to the integration of pain and associated cardiovascular responses induced by stress, fear and anxiety. Impairment in pain regulatory centers in painful conditions disturbs influence of CVS centers on pain control mechanisms.

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