

Electrical Stimulation And Pain Modulation

Andersen E. and Dafny N. (1983) An ascending serotonergic pain modulation pathway from the dorsal raphe nucleus to the parafascicularis nucleus of the thalamus. *Brain Res.* 269, 57-67.

Abstract: Three types of spontaneously active neurons were found in the parafascicularis (PF) nucleus of the thalamus of the rat: slow firing units (0.5-10 spikes/s), bursting units (2-5 spikes/burst in 10-20 ms, one burst every 1-2 s) and fast firing units (15-40 spikes/s). A similar population of neurons was found in the PF of rats treated with 5,7-dihydroxytryptamine (5,7-DHT), a serotonin neurotoxin. Noxious tail pinch (TP) caused 68% of the PF neurons to increase their firing rates to 242% of their initial baseline activity, while non-noxious touch stimulation failed to induce a response. In the 5,7-DHT-treated rats, TP caused 85% of the neurons in the PF to increase their firing rates to 581% of their initial baseline activity and 22% of the neurons increased their firing in response to touching the tail. Both the number of cells responding (P less than 0.05) and the percentage increase (P less than 0.001) were statistically greater in serotonin-depleted rats than in controls. This indicates that serotonin (5-HT) has a tonic inhibitory influence on responses to both noxious and non-noxious sensory stimuli. In control rats, electrical stimulation of the dorsal raphe nucleus (DR) decreased the firing rates of PF neurons. In contrast, the same DR stimulation induced an increase in PF firing rates during stimulation in serotonin-depleted rats and this increase in firing rates remained several seconds after cessation of stimulation. This indicates that the DR may use at least two different neurotransmitters in its projections to forebrain structures. In control rats, the TP stimulation induced an increase in firing rates of rates of PF neurons while DR stimulation attenuated the excitation induced by TP stimulation. In serotonin-depleted rats, DR stimulation and TP both caused an increase in firing rates. This effect was not additive indicating that there may be a serotonergic projection from the DR to the PF which modifies responses to somatosensory stimuli. The inhibitory effects elicited by electrical stimulation were limited to the immediate area of the DR. Stimulation of the adjacent reticular formation 1 mm lateral to the DR produced the opposite effect, an increase in firing rate often accompanied by driven spike activity in the PF

Andersen E. (1986) Periaqueductal gray and cerebral cortex modulate responses of medial thalamic neurons to noxious stimulation. *Brain Res.* 375, 30-36.

Abstract: The response of medial thalamic neurons to noxious peripheral stimulation were studied with intracellular recording methods in the cat. Electrical stimulation of the contralateral forepaw produced an EPSP-IPSP sequence followed by rebound excitation in these medial thalamic neurons. Action potentials appeared with the initial EPSP or with the rebound excitation. The mean latency to onset was 15 ms for the EPSP and 33 ms for IPSP. In contrast, electrical stimulation of the PAG or of the pericruciate cerebral cortex produced large IPSPs in the medial thalamic neurons. When PAG or cortex stimulation were paired with noxious stimulation, both the PAG and cortex responses predominated over the noxious response. This shows that the PAG and the cerebral cortex have the capabilities of influencing the responses of the medial thalamus to noxious stimulation. The medial thalamus is part of the relay system which sends information about noxious stimulation to the cerebral cortex where the noxious information reaches conscious awareness, so influencing the message at the level of the medial thalamus would probably alter the conscious perception of pain. The data suggest the existence of an ascending pain modulation

system from the midbrain to the thalamus and also suggests a mechanism of cortical control over pain perception

Carr K.D. and Bak T.H. (1988) Medial thalamic injection of opioid agonists: mu-agonist increases while kappa-agonist decreases stimulus thresholds for pain and reward. *Brain Res.* 441, 173-184.

Abstract: Selective agonists for mu- and kappa-opioid receptor types were infused, bilaterally, into the intralaminar central lateral nucleus of the rat. Subcataleptic doses of the mu-agonist, DAGO (0.25 and 1.0 microgram), elevated tailshock threshold for eliciting pain vocalization and motor responses. The hyperalgesic effect of U50,488 is not likely to be the result of antagonist action at a mu 2-isoreceptor; the general mu-antagonist, naloxone, and its less lipophilic quaternary analogue, both failed to produce a significant reduction in pain thresholds. Paralleling their effects on pain, DAGO and U50,488 elevated and reduced, respectively, lateral hypothalamic electrical stimulation threshold for positive reinforcement. These results suggest that medial thalamic opioid mechanisms are not exclusively involved in pain modulation but may generally regulate the responsiveness of the organism to motivating stimuli. Moreover, mu- and kappa-receptors may mediate opposite behavioral effects of opioid peptides

Chen Y., Wang Y., and Yin Q. (1991) [The role of paraventricular nucleus of hypothalamus in acupuncture analgesia in rats]. *Zhen. Ci. Yan. Jiu.* 16, 32-38.

Abstract: Recent evidence has indicated that vasopressin (VP) can increase the pain threshold. It is not clear whether the paraventricular nucleus (PVN) of hypothalamus, which is one of the main nuclei that secrete VP in brain, is involved in the acupuncture analgesia (AA). The present study was designed to examine the role of PVN in AA. Experiments were carried out on Wistar rats using tail stimulation vocalization test to measure the pain threshold. The acupoints "Renzhong" and "Chengjiang" were selected for electroacupuncture. Electrical stimulation of PVN could increase significantly the pain threshold and enhance the effect of AA. On the contrary, electrolytical lesion of PVN could decrease the effect of AA obviously, which could be recovered by cerebroventricular injection (ICV) of 300 ng of arginine VP. Pretreatment with AVP- antiserum (ICV) could attenuate the effect of AA. These data indicated that PVN plays an important role in pain modulation and in the effect of AA. This role might be mediated by the VP-containing neurons in PVN

Chudler E.H. and Dong W.K. (1995) The role of the basal ganglia in nociception and pain. *Pain* 60, 3-38.

Abstract: The involvement of the basal ganglia in motor functions has been well studied. Recent neurophysiological, clinical and behavioral experiments indicate that the basal ganglia also process non-noxious and noxious somatosensory information. However, the functional significance of somatosensory information processing within the basal ganglia is not well understood. This review explores the role of the striatum, globus pallidus and substantia nigra in nociceptive sensorimotor integration and suggests several roles of these basal ganglia structures in nociception and pain. Electrophysiological experiments have detailed the non-nociceptive and nociceptive response properties of basal ganglia neurons. Most studies agree that some neurons within the basal ganglia encode stimulus intensity. However, these neurons do not appear to encode stimulus location since the receptive fields of these cells are large. Many basal ganglia neurons responsive to somatosensory stimulation are activated exclusively or differentially by noxious stimulation. Indirect techniques used to

measure neuronal activity (i.e., positron emission tomography and 2-deoxyglucose methods) also indicate that the basal ganglia are activated differentially by noxious stimulation. Neuroanatomical experiments suggest several pathways by which nociceptive information may reach the basal ganglia. Neuroanatomical studies have also indicated that the basal ganglia are rich in many different neuroactive chemicals that may be involved in the modulation of nociceptive information. Microinjection of opiates, dopamine and gamma-aminobutyric acid (GABA) into the basal ganglia have varied effects on pain behavior. Administration of these neurochemicals into the basal ganglia affects supraspinal pain behaviors more consistently than spinal reflexive behaviors. The reduction of pain behavior following electrical stimulation of the substantia nigra and caudate nucleus provides additional evidence for a role of the basal ganglia in pain modulation. Some patients with basal ganglia disease (e.g., Parkinson's disease, Huntington's disease) have alterations in pain sensation in addition to motor abnormalities. Frequently, these patients have intermittent pain that is difficult to localize. Collectively, these data suggest that the basal ganglia may be involved in the (1) sensory-discriminative dimension of pain, (2) affective dimension of pain, (3) cognitive dimension of pain, (4) modulation of nociceptive information and (5) sensory gating of nociceptive information to higher motor areas. Further experiments that correlate neuronal discharge activity with stimulus intensity and escape behavior in operantly conditioned animals are necessary to fully understand how the basal ganglia are involved in nociceptive sensorimotor integration

Condes-Lara M. (1998) Different direct pathways of locus coeruleus to medial prefrontal cortex and centrolateral thalamic nucleus: electrical stimulation effects on the evoked responses to nociceptive peripheral stimulation. *Eur. J. Pain* 2, 15-23.

Abstract: Projections from the locus coeruleus (LC) to the centrolateral thalamus (Cl) and the medial prefrontal cortex (PFCx) were studied using orthodromic and antidromic stimulation techniques. The LC is a major noradrenergic source in the central nervous system, and its descending projections provide an important source of pain suppression at spinal level. Previously, the author has described a cortico-thalamic loop involved in pain modulation. The present paper reports on a study of the participation of LC as part of an ascending pain-control system acting on the cortico-thalamic loop. Rats were anaesthetized with halothane, and single unit recordings were made in LC using glass micropipettes. Stainless steel electrodes were placed in cortex and thalamus for electrical stimulation. Stimulation in PFCx or Cl produces antidromic responses in neurons in LC. The latencies, conduction velocity and location of neurons in LC projecting to PFCx or Cl structures are described. Separate projections to both structures have significantly different conducting velocities, arriving earlier at Cl (mean conduction velocities 0.27 and standard deviation +/-0.06 m/s) and then at PFCx (mean conduction velocities 0.20 +/- 0.04 m/s). The presence of orthodromic responses suggests reciprocal connections. The paper also describes the suppression of spontaneous and nociceptive- evoked activity in the PFCx and Cl following electrical stimulation in LC. It is proposed that the LC innervation could be associated with an ascending noradrenergic system acting upon a Cl-PFCx pain-modulation mechanism. Copyright 1998 European Federation of Chapters of the International Association for the Study of Pain

Dafny N., Dong W.Q., Prieto-Gomez C., Reyes-Vazquez C., Stanford J., and Qiao J.T. (1996) Lateral hypothalamus: site involved in pain modulation. *Neuroscience* 70, 449-460.

Abstract: The present study is an attempt to examine the neuronal circuitry of a

supraspinal site engaged in pain modulation. Five physiological measures were postulated as the criteria for defining a central nervous system site engaged in the circuitry of pain modulation. The lateral hypothalamus met these five measures: (i) 81% of the lateral hypothalamus neurons (247/304) responded to noxious stimuli using a single cell recording procedure; (ii) stimulation of the periaqueductal gray-dorsal raphe area or the habenula modulated 98% and 87% of the lateral hypothalamus noxious-evoked activity; (iii) microiontophoretically applied morphine modulated 77% of the lateral hypothalamus noxious evoked activity; (iv) electrical stimulation of the lateral hypothalamus produced behavioral analgesia proportional to the stimulus intensity as assessed by the tail flick assay; and (v) morphine application into the lateral hypothalamus produced behavioral analgesia in a dose-response manner using the tail flick assay. In conclusion, the lateral hypothalamus can be considered one of the pain modulation sites

Dong W.Q., Qiao J.T., Skolnick M., and Dafny N. (1991) Focal dorsal raphe stimulation and pinnal electrical stimulation modulate spontaneous and noxious evoked responses in thalamic neurons. *Int. J. Neurosci.* 57, 123-140.

Abstract: This study investigated the nociceptive responses of single neurons within the nucleus parafascicularis (PF) thalami of the rat following two modes of electrical stimulation known to induce analgesia. It was found that both focal electrical dorsal raphe stimulation (DRS) and bilateral pinnal (ear) electrical stimulation (PES) converge on the same PF neurons, affecting both the spontaneous discharges and the noxious evoked responses toward these neurons. The effects of different stimulus current intensity, frequency and pulse duration were also examined. It was found that for both DRS and PES at pulse frequency of 10 Hz and current amplitude of 10 microA are the optimal parameters to modulate both the spontaneous and the noxious evoked responses. These stimuli produced prolonged effects related to the duration of stimulation. The external (PES) low current stimulation which was delivered below the sensory threshold was as effective in modulating noxious responses as the invasive DRS in intact animals and in animals with bilateral dorsolateral-funiculus ablation. It was observed that dorsal lateral funiculus ablation (DLFx) did not modify the DRS and the PES effects. These observations further support the existence of an ascending pain modulation pathway

Ennis M., Behbehani M., Shipley M.T., Van Bockstaele E.J., and Aston-Jones G. (1991) Projections from the periaqueductal gray to the rostromedial pericoerulear region and nucleus locus coeruleus: anatomic and physiologic studies. *J. Comp Neurol.* 306, 480-494.

Abstract: Previous studies showed that the nucleus locus coeruleus (LC) receives two major afferent inputs from 1) nucleus paragigantocellularis and 2) nucleus prepositus hypoglossi, both in the rostral medulla. Recent reports suggested that the midbrain periaqueductal gray (PAG) projects to the rostromedial pericoerulear area and LC. Since the PAG is a major site for control of central antinociception, and since descending noradrenergic fibers have been implicated in pain modulation, we have investigated in detail the functional anatomy of projections from PAG to the dorsolateral pontine tegmentum. A combined anatomical and electrophysiological approach was used to assess the organization and synaptic influence of PAG on neurons in the rostromedial pericoerulear region and in LC proper. Injections of the tracer wheatgerm agglutinin conjugated to horseradish peroxidase encompassing LC proper and the rostromedial pericoerulear area retrogradely labeled neurons in PAG located lateral and ventrolateral to the cerebral aqueduct; injections restricted to LC

proper did not consistently label PAG neurons. Deposits of the anterograde axonal tracer Phaseolus vulgaris leucoagglutinin into this same region of PAG labeled axons that robustly innervated the zone rostral and medial to LC. Only sparse fibers were observed in LC proper. Consistent with these results, focal electrical stimulation of LC antidromically activated only a few PAG neurons (6 of 100); all of these driven cells were located lateral and ventrolateral to the cerebral aqueduct. The majority of neurons in the rostromedial pericoerulear area were robustly activated by single pulse stimulation of PAG. In contrast, single pulse electrical stimulation of lateral PAG produced weak to moderate synaptic activation of some LC neurons; stimulation of ventrolateral PAG produced predominant inhibition of LC discharge, perhaps through recurrent collaterals subsequent to antidromic activation of neighboring LC cells. Taken together, these results indicate that PAG strongly innervates the region rostral and medial to LC, including Barrington's nucleus, but only weakly innervates LC proper. Although recent studies indicate that the dendrites of LC neurons ramify heavily and selectively in the rostromedial pericoerulear region, the results of the present physiological studies suggest that PAG preferentially targets rostromedial pericoerulear neurons rather than LC dendrites

Fardin V., Oliveras J.L., and Besson J.M. (1984) A reinvestigation of the analgesic effects induced by stimulation of the periaqueductal gray matter in the rat. II. Differential characteristics of the analgesia induced by ventral and dorsal PAG stimulation. *Brain Res.* 306, 125-139.

Abstract: This study consists of a detailed analysis of the analgesic effects induced by stimulation of the various parts of the periaqueductal gray matter (PAG) in the freely moving rat. In order to characterize the analgesia, two criteria are considered: (1) the evaluation of the degree of analgesia and behavioral side effects evoked during central stimulation; and (2) the presence of post-effects. Central stimulation (50 Hz sine waves) was delivered via bipolar concentric electrodes and analgesia was quantified by the change in the vocalization threshold induced by electrical stimulation of the tail. Within the ventral PAG, the vocalization threshold increased gradually with the intensity of the central stimulation, the degree of analgesia generally being powerful. There was no relationship between the strength of the analgesic effects and the motor disturbances also produced by stimulation of this region. Antinociceptive effects generally disappeared when the stimulation ceased. Only when the intensity of the stimulation was strong enough to induce very powerful analgesic effects were post-stimulation analgesic effects noticed. Within the dorsal and dorsolateral PAG as well as in the ventral region just surrounding the aqueduct, analgesia appeared suddenly, was generally less pronounced and was always concomitant with strong aversive reactions. In contrast with the analgesia from the ventral PAG, marked post-effects were observed. These latter characteristics were also obtained from stimulation of regions located outside the PAG (colliculi, intercollicular commissure and tectum adjacent to the dorsolateral PAG) although these zones were not extensively studied. By consideration of various data in the literature, it is concluded from this study, which clearly distinguishes stimulation-produced-analgesia (SPA) from ventral PAG versus dorsal PAG, that analgesia induced from this midbrain area involves at least two different neuronal substrates. Whilst the ventral PAG seems to be more preferentially involved in pain modulation, the authenticity of 'analgesia' triggered by stimulation of aversive regions (which are widely spread over the PAG) is questioned and proposals to explain the simultaneous appearance of analgesic effects and aversion are considered

Herz A. and Millan M. (1989) [Participation of opioids and opioid receptors in antinociception at various levels of the nervous system]. *Farmakol. Toksikol.* 52, 5-12.

Abstract: At the cerebral level, studies employing several experimental approaches point to an essential role of beta-endorphin in analgesia, induced by electrical stimulation of the periaqueductal grey of the midbrain. Tolerance and cross-tolerance studies suggest that mu-opioid receptors mediate this effect. The significance of s

Herz A. and Millan M.J. (1990) Opioids and opioid receptors mediating antinociception at various levels of the neuraxis. *Physiol Bohemoslov.* 39, 395-401.

Abstract: One of the central issues in present experimental pain research is to establish the identity, location, and mechanism of action of various opioids (opioid peptides and alkaloids) and multiple opioid receptors in the modulation of nociceptive processes. At the cerebral level, studies employing several experimental approaches point to an essential role of beta-endorphin in analgesia, induced by electrical stimulation of the periaqueductal grey of the midbrain. Tolerance and cross-tolerance studies suggest that mu-opioid receptors mediate this effect. The significance of d

Ignelzi R.J. and Nyquist J.K. (1979) Excitability changes in peripheral nerve fibers after repetitive electrical stimulation. Implications in pain modulation. *J. Neurosurg.* 51, 824-833.

Abstract: The Melzack-Wall gate control theory has been invoked to explain the peripheral analgesia resulting from repetitive electrical stimulation of peripheral nerve. This model emphasizes presynaptic inhibitory interactions among afferent fiber terminals in the spinal cord. An alternative explanation, that of velocity change in peripheral nerve fiber conduction, has been suggested by compound action potential studies from our laboratory. The present study was designed to extend this work, and to investigate the single fiber changes subsequent to brief (5- to 20-minute) periods of repetitive, high frequency (180 to 200/sec) electrical stimulation through an implantable peripheral nerve cuff device of the type used clinically for pain relief. Most fibers, regardless of their diameter (estimated from conduction velocity), show one or more of the following characteristics: a transient slowing of conduction velocity, an increase in electrical threshold and/or a decrease in response probability following a period of repetitive electrical stimulation. This supports the hypothesis that there are changes in direct peripheral nerve fiber excitability occurring under conditions simulating clinical electroanalgesia

Ignelzi R.J. and Atkinson J.H. (1980) Pain and its modulation. Part 2. efferent mechanisms. *Neurosurgery* 6, 584-590.

Abstract: Recent studies of central nervous system effects on pain and on its efferent modulation have created new theories and have led to direct clinical applications that may in time eclipse more classical interventions. In this review electrical stimulation analgesia is presented as a paradigm of how basic science work has been applied clinically to produce some of the most exciting advances in recent years in the treatment of chronic pain. Opiate receptors and analgesia are presented in relationship to the descending inhibitory systems used in electroanalgesia. Neuromodulators and neurotransmitters important in pain modulation through complex inhibitory and excitatory pathways are discussed, with the roles of B-endorphin, enkephalin, serotonin, and other important biogenic amines being stressed. The neuropharmacology of pain as it is currently understood clinically

suggests that psychotropic interventions may be quite useful in treating difficult pain problems

Krainick J.U. and Thoden U. (1976) [Methods of pain modulation by electrical stimulation (author's transl)]. *Langenbecks Arch. Chir* 342, 75-81.

Abstract: Different methods of modulating pain by electrical stimulation are described: (1) Nondestructive transcutaneous nerve stimulation is recommended for neurogenic pain syndromes prior to other procedures (success rate about 30%); (2) The implantation of electrodes on the dorsal columns yields good effects in 65% after careful selection; (3) First results with implantations in deep brain structures are discussed

Landau B. and Levy R.M. (1993) Neuromodulation techniques for medically refractory chronic pain. *Annu. Rev. Med.* 44, 279-287.

Abstract: Advances in our knowledge of the physiology of pain transmission and modulation have created new surgical options for the control of chronic pain. The pain modulation network can be activated by administration of spinal opiates or by electrical stimulation of the nervous system with transcutaneous, peripheral nerve, spinal cord, and deep brain stimulation. The theoretical basis and the clinical applications of neurostimulation for the treatment of medically intractable chronic pain are reviewed

Moyanova S. and Ta L. (1988) Dorsal raphe stimulation modulates responses of substantia nigra, pars reticulata neurons to painful stimulation. *Acta Physiol Pharmacol. Bulg.* 14, 24-32.

Abstract: There are but few data that substantia nigra neurons are involved in the pain-processing mechanisms in the CNS. In contrast, a great deal of evidence suggests a participation of the dorsal raphe nucleus (RD) in these processes. The purpose of the present study was to examine the effects of painful stimulation (suprathreshold electrical stimulation of the peroneal nerve--NP) on the extracellular activity of neurons of substantia nigra, pars reticulata (SNR) in cats, and to determine if a train of stimuli applied to RD could affect the responses of SNR neurons to this type of painful stimulation. The majority of SNR neurons (83.3%) responded to NP-stimulation either with an increase or with a decrease in the firing rate. The RD-stimulation when applied simultaneously or just before the NP-stimulation reduced or even eliminated the increase in the firing rate caused by pain irrespective of the ability of RD-stimulation applied previously alone to reduce or not the spontaneous activity of the SNR neurons. In cells which responded with inhibition to NP- and RD-stimulations when applied alone, RD-stimulation applied just before NP-stimulation slightly prolonged the NP-induced inhibition. The results indicate that in addition to the descending pain modulation pathway from the dorsal raphe nucleus to the spinal cord, which pathway is well established, there may be an ascending one to some supraspinal structures, the substantia nigra being one of them

Vignocchi G., Murri L., Rossi B., Rosa C., and Ghione S. (1989) Correlation between pain thresholds and polysynaptic components of blink reflex in essential arterial hypertension. *Funct. Neurol.* 4, 59-61.

Abstract: An interaction between pain modulation and arterial pressure control has been proposed on the basis of experimental data in man and animal. Eight hypertensive patients and eight normotensive volunteers were investigated by electrical stimulation of the first trigeminal branch and dental pulp, to evaluate

nociceptive sensation and reflex responses. A significant threshold increase of pain sensation and R2, R3 polysynaptic components of the blink reflex, has been found in hypertensive patients

Walker J.M., Huang S.M., Strangman N.M., Tsou K., and Sanudo-Pena M.C. (1999) Pain modulation by release of the endogenous cannabinoid anandamide. Proc. Natl. Acad. Sci. U. S. A 96, 12198-12203.

Abstract: Synthetic cannabinoids produce behavioral analgesia and suppress pain neurotransmission, raising the possibility that endogenous cannabinoids serve naturally to modulate pain. Here, the development of a sensitive method for measuring cannabinoids by atmospheric pressure-chemical ionization mass spectrometry permitted measurement of the release of the endogenous cannabinoid anandamide in the periaqueductal gray (PAG) by in vivo microdialysis in the rat. Electrical stimulation of the dorsal and lateral PAG produced CB1 cannabinoid receptor-mediated analgesia accompanied by a marked increase in the release of anandamide in the PAG, suggesting that endogenous anandamide mediates the behavioral analgesia. Furthermore, pain triggered by subcutaneous injections of the chemical irritant formalin substantially increased the release of anandamide in the PAG. These findings indicate that the endogenous cannabinoid anandamide plays an important role in a cannabinergic pain-suppression system existing within the dorsal and lateral PAG. The existence of a cannabinergic pain-modulatory system may have relevance for the treatment of pain, particularly in instances where opiates are ineffective

Xiong K. and Zheng P. (1990) [The effect of the septal area in acupuncture analgesia]. Zhen. Ci. Yan. Jiu. 15, 1-5, 12.

Abstract: This review summarized some articles on the effect of the septal area in acupuncture analgesia. The data showed that the pain threshold of animal was increased when septal area was stimulated by electro- acupuncture, and that electrical stimulation of septal area had a marked inhibitory effect on the pain discharges of cells in parafascicular nucleus of thalamus, lateral habenular nucleus, periaqueductal gray and dorsal raphe nucleus. The septal area play an important role in acupuncture analgesia. The majority of the cholinergic neurons in septal area are located in nucleus of the vertical limb of the diagonal band (VDB); gamma-aminobutyric acid of septal area is mainly found in the diagonal band nucleus(td); Dopamine is present in high levels in td and lateral septal nucleus(S1) of septal area; The S1 contain high densities enkephalin-containing neuronal cell bodies and terminals; In addition, substance P and norepinephrine are also high levels in the septal area. These substance above-mentioned have a relations with acupuncture analgesia of septal area. A large number of serotonin-containing neurons are found in the raphe nuclei. The serotonin play an important role in acupuncture analgesia. The serotonin-containing neurons in dorsal raphe nucleus project to S1. The fiber connections of the raphe nuclei with the td are reciprocation. The periaqueductal gray is a important structure on pain modulation. It projects to septal area and receives the fibers from S1. A number of adrenergic neurons are located within the locus coeruleus. The locus coeruleus participate pain modulation and acupuncture analgesia. The neuro-anatomy study demonstrated that locus coeruleus projects to septal area.(ABSTRACT TRUNCATED AT 250 WORDS)

Zemlan F.P. and Behbehani M.M. (1988) Nucleus cuneiformis and pain modulation: anatomy and behavioral pharmacology. Brain Res. 453, 89-102.

Abstract: The anatomical substrate and behavioral pharmacology of stimulation-produced analgesia resulting from electrical stimulation of the pontomesencephalic nucleus cuneiformis (NCF) was determined in the present study. Maximum increase in nociceptive tail-flick latencies following NCF stimulation occurred during the first 5 min post stimulation and decreased afterwards. The increased reflex latency could be attenuated by prior treatment with the narcotic antagonist, naloxone or the cholinergic antagonist, scopolamine. The anatomical projections of NCF were identified in autoradiographic and histochemical studies. Ipsilateral fibers coursed caudal from the NCF injection site through the ventral pontine reticular formation to innervate nucleus raphe magnus and the ipsilateral nucleus magnocellularis. At rostral medullary levels fibers coursed dorsolateral to innervate the ipsilateral nucleus reticularis parvocellularis. Descending contralateral fibers crossed through the decussation of the superior cerebellar peduncle, then coursed ventrolaterally projecting to the contralateral nucleus magnocellularis. Two primary groups of ascending fibers were observed. The dorsally located group ascended through the central tegmental tract projecting to the dorsal raphe, ipsilateral periaqueductal gray, nucleus parafascicularis and centromedianus, the intermediolateral and lateral thalamic nuclei. The ventral group coursed ventrolateral from the injection site projecting to the substantia nigra, zona compacta, ventral tegmental area of Tsai, zona incerta, Fields of Forel, lateral hypothalamic nucleus and nucleus reuniens. These anatomic and behavioral data suggest that NCF plays an important role in sensory/motor integration relevant to pain transmission

Zhang S., Tang J.S., Yuan B., and Jia H. (1998) Inhibitory effects of electrical stimulation of ventrolateral orbital cortex on the rat jaw-opening reflex. *Brain Res.* 813, 359-366. **Abstract:** In previous studies, we have shown that electrically or chemically evoked activation of the ventrolateral orbital cortex (VLO) depresses the rat tail-flick (TF) reflex, and this antinociceptive effect is mediated by the periaqueductal gray (PAG). The aim of the present study was to examine whether electrical stimulation of the VLO could inhibit the rat jaw-opening reflex (JOR), and to determine whether electrolytic lesions of the PAG could attenuate this VLO-evoked inhibition. Unilateral electrical stimulation of the VLO significantly depressed the JOR elicited by tooth pulp or facial skin stimuli, with a mean threshold of 30.5 ± 2.3 microA ($n=22$). Increasing stimulation intensities from 30 to 80 microA resulted in greater reduction of the dEMG amplitude from $22.9 \pm 5.0\%$ to $69.7 \pm 3.7\%$ of the baseline value ($P < 0.01$, $n=22$). The inhibitory effect appeared 50 ms after the beginning of VLO stimulation and lasted about 150 ms, as determined by varying the conditioning-test (C-T) time interval. Unilateral lateral or ventrolateral lesions of the PAG produced only a small attenuation of the VLO-evoked inhibition of the JOR, but bilateral lesions eliminated this inhibition. These findings suggest that the VLO plays an important role in modulation of orofacial nociceptive inputs, and provide further support for the hypothesis that the antinociceptive effect of VLO is mediated by PAG leading to activation of a brainstem descending inhibitory system and depression of nociceptive inputs at the trigeminal level. The role played by VLO in pain modulation is discussed in association with the proposed endogenous analgesic system consisting of medullary cord-Sm-VLO-PAG-medullary cord

Zhang Y.Q., Tang J.S., Yuan B., and Jia H. (1995) Effects of thalamic nucleus submedius lesions on the tail flick reflex inhibition evoked by hindlimb electrical stimulation in the rat. *Neuroreport* 6, 1237-1240. **Abstract:** Bilateral electrolytic lesions of the thalamic nucleus submedius (Sm)

facilitated the TF reflex and attenuated the antinociception evoked by hindlimb electrical stimulation with high intensities in lightly anaesthetized rats. However, the antinociception produced by low intensity hindlimb stimulation was unchanged, except that the after- effect was reduced. The results show that the Sm is probably involved in pain modulation and plays an important role in mediation of the antinociception elicited by high intensity peripheral stimulation

Zhang Y.Q., Tang J.S., Yuan B., and Jia H. (1997) Inhibitory effects of electrically evoked activation of ventrolateral orbital cortex on the tail-flick reflex are mediated by periaqueductal gray in rats. *Pain* 72, 127-135.

Abstract: The present study found in lightly anesthetized rats that the radiant heat-evoked tail flick (TF) reflex was markedly inhibited by a unilateral electrical stimulation (a 20 ms train of 0.2 ms, 100 Hz, 30- 100 microA pulses) of the ventrolateral orbital cortex (VLO), with the tail flick latency (TFL) being increased. The mean threshold of VLO stimulation for producing inhibition of the TF reflex was 39.2 +/- 8.7 microA (n = 26), and this inhibitory effect increased following increasing stimulation intensity from 40 to 70 microA. The inhibition developed and remained during the stimulation and disappeared rapidly after termination of the stimulation. When the VLO was stimulated at an intensity of 100 microA in addition to the inhibition an after- facilitation of the TF reflex (a decrease in TFL) was observed at 5-10 s after termination of the stimulation. Bilateral electrolytic lesions of the lateral or ventrolateral parts of the periaqueductal gray matter (PAG) dramatically reduced or eliminated the VLO-evoked inhibition, and the after-facilitation as well. The difference was significant between the TFL changes produced by VLO stimulation before and after PAG lesion ($P < 0.01$). The results suggest that the antinociception elicited by VLO stimulation is mediated by PAG, leading to activation of the brainstem descending inhibitory system which depresses the nociceptive transmission at the spinal level. The role played by VLO in pain modulation was discussed in association with the proposed endogenous analgesic system consisting of spinal cord-Sm-VLO-PAG-spinal cord