Medical Hypotheses (2000) **55**(4), 283–288

doi: 10.1054/mehy.1999.1031, available online at http://www.idealibrary.com on IDEAL®

DL-phenylalanine markedly potentiates opiate analgesia – an example of nutrient/pharmaceutical up-regulation of the endogenous analgesia system

A. L. Russell[1], M. F. McCarty[2]

[1]Brampton Pain Clinic, Bramalea, Ontario, Canada [2]Pantox Laboratories, San Diego, CA, USA

Summary In the author's clinical experience, concurrent treatment with DL-phenylalanine (DLPA) often appears to potentiate pain relief and also ease depression in patients receiving opiates for chronic non-malignant pain. An analysis of this phenomenon suggests that it may be mediated, at least in part, by up-regulation of the 'endogenous analgesia system' (EAS), a neural pathway that projects caudally from medullary nuclei to the dorsal horn of the spinal column; when stimulated by chronic pain or therapeutic measures such as opiates or acupuncture, the EAS suppresses activation of second-order pain-receptive neurons in the dorsal horn, and thereby alleviates pain. Since serotonin and enkephalins are key neurotransmitters in the EAS, it is reasonable to predict that measures which promote serotonin activity (such as 5-hydroxytryptophan and serotonin-reuptake inhibitors) as well as enkephalin activity (such as D-phenylalanine, an enkephalinase inhibitor) should potentiate EAS-mediated analgesia – a view consistent with much previous medical research. Comprehensive support of the EAS with well-tolerated nutrients and pharmaceuticals may amplify the analgesic efficacy of chronic opiate therapy, while enabling dosage reductions that minimize opiate side-effects. Analogously, this approach may complement the efficacy of acupuncture and other analgesic measures that activate the EAS. © 2000 Harcourt Publishers Ltd

> *Among the remedies that it has pleased Almighty God to give to man to relieve his suffering, none is so universal and so efficacious as opium.* (Thomas Sydenham, Physician, 1680)

DLPA AS AN ADJUVANT TO MORPHINE IN CHRONIC NON-MALIGNANT PAIN

Over the past decade, the management of chronic pain due to malignancy has improved greatly with the use of adequate doses of analgesics, especially narcotics. It is in the management of chronic non-malignant pain (CNMP) that we have failed in the majority of cases. In most patients with CNMP a correctable cause is not found, and the patient is faced with years, if not decades, of very intrusive chronic pain. In the last decade, attention has been focused on the use of slow-release oral opiates, the impetus being provided by the work of Portenoy and Foley (1). These authors have noted that, whereas most patients can obtain some relief with this strategy, a fortunate minority can be benefited to the extent that they can return to a more normal lifestyle. Although these patients typically develop opiate dependency, they do not become

Received 17 March 1999
Accepted 18 October 1999

Correspondence to: Alan L. Russell, Brampton Pain Clinic, 18 Kensington Road, Suite 201, Bramalea, Ontario, Canada

addicted in the way that drug abusers often do. Constipation, nausea, and sedation can be dose-limiting side effects of slow-release opiate therapy. However, a more important factor limiting the use of this therapy for CNMP has been the (often warranted) fear that prescription of opiates for this purpose may subject the physician to legal harassment by over-zealous guardians of public morality. It is refreshing to note that certain medical associations in the U.S. and Canada have outlined rational guidelines for the use of opiates in CNMP (2), and other professional organizations are following suit.

Most physicians become extremely frustrated in dealing with CNMP, since its etiology is often uncertain and management difficult. In a world where physicians have become accustomed to 'magic bullet' therapeutics, CNMP patients are often ignored as an ongoing embarrassment revealing the limitations of modern medical practice. It is against this background that, ten years ago, the senior author (AR) became interested in pursuing the use of slow-release opiate therapy as proposed by Portenoy and others. My experience with this strategy has been reasonably gratifying. In particular, having treated in excess of 50 CNMP patients with narcotics, often in doses of long-acting morphine of 60 mg t.i.d., I have yet to encounter the bogeyman problems of addiction or tachyphylaxis. (Possibly, the addiction experienced by recreational drug abusers reflects the fact that they use bolus doses to achieve a 'high'; addiction may be less likely with moderate-dose, time-release medication such as that used for chronic pain control. In addition, it is conceivable that those who choose to abuse drugs have personality traits or subtle neurological dysfunctions that render them more prone to addiction.)

Nonetheless, this therapy often leaves something to be desired, both in regard to the pain relief achieved and side effects. For this reason, it is appropriate to search for adjuvants that could improve analgesic efficacy while perhaps enabling opiate dose reductions that would minimize side effects. In this regard, I was drawn to an evaluation of DL-phenylalanine (DLPA), in large part because of reports that it might have anti-depressant activity (3–6). The great majority of patients with CNMP are depressed due to the pain, difficulty in maintaining a job, marital problems, etc. Evidence that D-phenylalanine (DPA) has analgesic potential, possibly owing to its ability to inhibit enkephalinase (carboxypeptidase A), also motivated a trial of DLPA in my CNMP patients (7–11). DLPA is known to be safe and well tolerated (it has been on the 'generally recognized as safe' list of the US Food and Drug Administration for decades) and has not been reported to produce dependence.

I have observed that, as an adjunct to slow-release morphine therapy, DLPA in doses of 500–1000 t.i.d. has a quite evident beneficial impact on the depression associated with CNMP, and often improves the quality of pain control, sometimes enabling a reduction in the dose of morphine. The observation that DLPA has both antidepressant and analgesic action suggests that it may be ideally suited to the scenario of chronic pain. In light of the tremendous suffering and economic loss associated with chronic pain syndrome, controlled studies evaluating DLPA as an adjuvant therapy for this condition are urgently needed. Such studies will not arise without the dedicated efforts of humane medical scientists; pharmaceutical companies have no motivation to study or promote DLPA, which is unpatentable and already widely available as a 'nutritional supplement'.

A literature search on DPA's analgesic activity in animals yields both positive (7–11) and negative (10–12) reports. The only double-blind clinical evaluation of DPA (250 mg q.i.d.) as a monotherapy for chronic pain failed to demonstrate benefit (13). However, a number of researchers have concluded that DPA can potentiate acupuncture analgesia, both in animals and humans (7,14–18), lamentably, the clinical studies were not placebo-controlled. More to the point of my own observations is a German study demonstrating that DPA potentiates morphine analgesia in mice, such that equivalent pain control can be achieved with half the previous dose of morphine – enabling a reduction in morphine side effects (19). The present informal report may constitute the first clinical demonstration of this principle (albeit using DLPA). An overview suggests that, whereas DPA, at least in doses heretofore tested, has limited (if any) clinical value as a monotherapy, it may well be clinically useful as a potentiator of certain established analgesic measures such as opiates and acupuncture.

In regard to anti-depressant activity, one double-blind clinical trial, in which DLPA (150–200 mg daily) was compared to comparable doses of imipramine in patients with endogenous depression, concluded that response to these two agents did not differ over the 30 days of the study (6). Previous open studies with DPA or DLPA in comparable doses had likewise reported efficacy (3–5). On the other hand, a single-blind assessment of DPA in this disorder (median dose, 350 mg daily) failed to observe benefit (20). These studies may have limited relevance to my own observations; I have used a far higher dose (equivalent to 750–1500 mg DPA/day), and moreover I was not treating endogenous depression per se, but rather depression associated with chronic pain – no doubt a distinct depressive entity. It is conceivable that DLPA's analgesic effect was a key mediator of the antidepressant action reported here.

THE ENDOGENOUS ANALGESIA SYSTEM

The clinical efficacy of DLPA as an adjuvant analgesic measure may be rationalized by considering the role of

the 'endogenous analgesia system' (EAS) in pain perception (21–25). Whereas acute pain perception has critical survival value, chronic severe pain evidently is counterproductive; it is therefore not surprising that animals have evolved neural mechanisms for dampening the transmission of pain signals to higher brain centers. These pain signals are generated by small primary afferent fibers that pass through the dorsal root of the spinal column and synapse with 'second-order' neurons in the dorsal horn of the spinal gray matter. The axons of these second-order neurons, after crossing contralaterally, ascend through the spinothalamic tract to synapse with 'third-order' neurons in the thalamus; the thalamus then integrates the signal and relays it to the cortex. The concept of an EAS arose from the discovery that stimulation of certain supraspinal nuclei – notably the periaqueductal gray (PAG) in the midbrain and, more caudally, the nucleus raphe magnus (NRM) and the nucleus reticularis paragigantocellularis (NRPG) in the rostral ventromedial medulla (RVM) – blocks the activation of second-order pain-receptive neurons in the dorsal horn. Neuroanatomical studies revealed that these nuclei send axons caudally, primarily through the dorsolateral funiculus, to form synapses in the dorsal horn. These synapses release serotonin or norepinephrine, and intrathecal administration of either methysergide or yohimbine (a specific alpha-2 antagonist) suppresses the analgesic activity of the EAS (23). However, intrathecal naloxone also has this effect; apparently, the dorsal horn projections of the PAG and RVM activate opioid interneurons which then act both pre-synaptically and post-synaptically to inhibit activation of second-order pain-receptive neurons (25). (Endorphins typically act as hyperpolarizing inhibitory neurotransmitters.) Although the PAG sends some axons directly to the spinal column, its analgesic activity is chiefly mediated by shorter axons that activate the NRM and NRPG. Stimulation of certain brain centers rostral to the PAG can also elicit analgesia, but these effects appear to be mediated via neural connections to the PAG. Thus, the PAG and the RVM nuclei are of central importance in the EAS.

What is the physiological role of this EAS? The PAG, NRM and NRPG all receive activating afferents from the spinothalamic tract – thus creating a feedback loop that can dampen pain transmission. The PAG also receives inputs from a number of higher centers, including the cortex and hypothalamus; this enables regulation of pain perception by a variety of complex integrated signals. These mechanisms possibly account for the well-known phenomenon that soldiers seriously injured in the heat of battle often initially experience relatively little pain. Stress-induced analgesia in rodents appears to be mediated by the EAS (22); analgesia during and following strenuous exercise ('runner's high') may be a variant of this.

THE EAS AS A TARGET FOR ANALGESIC THERAPY

Microinjection of morphine into the PAG, NRM, or NRPG triggers analgesia by activating neurons projecting to the dorsal horn (22,24). (This activation is indirect; it is thought that morphine or endogenous opiates inhibit the activity of interneurons that tonically inhibit the neurons projecting to the dorsal horn.) Intriguingly and importantly, the chief analgesic effect of systemically-administered morphine results from activation of the PAG, as demonstrated by the fact that microinjection of naloxone into the PAG blocks most of the analgesic activity of systemic morphine (22); evidently, the PAG is exquisitely sensitive to exogenous opiates. This implies that systemic morphine controls pain primarily by indirectly promoting release of endogenous opiates in the dorsal horn, rather than by a direct action on opioid receptors in this region.

Chinese scientists have demonstrated that electroacupuncture likewise achieves its longer-lasting analgesic effects by activating the EAS; more specifically, they find that electrical stimulation of certain traditional acupuncture points activates the NRM and promotes the expression of c-fos in this nucleus (26,27). The analgesia evoked by transcranial electrostimulation, inasmuch as it is naloxone-inhibitable and potentiated by serotonin precursors and enkephalinase inhibitors, may also be mediated by the EAS (28–31). In contrast, the acute analgesia evoked by high-frequency transcutaneous electrical neurostimulation (TENS) is not naloxone-suppressible and appears to reflect a local 'gating' mechanism independent of supraspinal influences; however, some reports indicate that, at lower frequencies, naloxone can indeed inhibit TENS analgesia (32–37).

Very recently, the analgesic effects of cannabinoids in rats have been shown to reflect activation of RVN nuclei; this activation is not mediated by release of opioids in the RVN, and thus is potentially complementary to the effects of opiates (38). Moreover, endogenous cannabinoids appear to exert a tonic up-regulatory influence on the EAS, as demonstrated by the hyperalgesia elicited by microinjection of a cannabinoid antagonist into the RVN. Thus, if low-dose or synthetic cannabinoids can be developed as practical analgesic therapies, they will represent yet another means of controlling pain by EAS stimulation.

PRACTICAL POTENTIATION OF THE EAS

In light of the prominent roles of serotonin and enkephalins as mediators of the EAS, it can readily be predicted that certain agents will potentiate EAS activity. Enkephalinase inhibitors – of which D-phenylalanine is an example – can be expected to amplify the activity of enkephalins released in the dorsal horn, and also to

modestly up-regulate activation of the PAG, NRM and NRPG by potentiating their endogenous opioid activity. Since supplemental tryptophan or 5-hydroxytryptophan enhances serotonin synthesis by increasing precursor availability (39,40), these agents should potentiate the dorsal horn serotonin release resulting from EAS activation. Drugs or herbs that inhibit serotonin reuptake mechanisms might be expected to have a similar effect. Whether tyrosine administration would enhance the noradrenergic component of EAS activity is more difficult to predict, as tyrosine availability is usually only rate-limiting for tyrosine hydroxylase activity in neurons that are highly active (41).

These predictions appear to be borne out in animal and clinical studies. D-phenylalanine, or other enkephalinase inhibitors, are reported to potentiate the analgesia evoked by morphine, acupuncture, TENS, cannabinoids, antidepressants, and stress (7,14–19,29,42–45). Analogous activity has been reported for tryptophan/5-hydroxytryptophan as well as for antidepressants that primarily influence serotonergic activity; these agents also have some analgesic activity as monotherapies (31,43,46–61). Reversal of clinical opiate resistance has been observed following tryptophan administration (47). In rats, tyrosine or its methylester do indeed potentiate morphine analgesia, although this effect appears to be mediated supraspinally rather than in the dorsal horn (62,63).

These considerations suggest that the apparent utility of DLPA as an adjuvant to opiate therapy is just a specific example of a more general therapeutic opportunity – well-tolerated agents which potentiate the activity of serotonin and enkephalins should be used in conjunction with analgesic therapies whose efficacy is mediated primarily by EAS activation. These therapies include not only opiates, but also acupuncture, transcranial electrostimulation, and cannabinoids. This strategy has the potential to provide superior pain relief, reverse opiate resistance, and enable reductions in the dose (and thus side effects) of opiates or other analgesic drugs.

The adjuvant measures suggested here could also likely have the merit of alleviating the depression that frequently accompanies chronic severe pain. This is obviously true in regard to serotonin-potentiating measures. Whether or not DLPA has general antidepressant activity, the clinical observations reported above support its utility in the depression associated with chronic pain.

Inasmuch as 5-hydroxytryptophan is highly effective for boosting serotonin synthesis, serotonin-evoked GI spasm and diarrhea are the chief side effects which limit the feasible oral dose of this agent (64). In contrast, constipation reflecting GI hypomotility is one of the major complaints of opiate-treated patients. This suggests the appealing possibility that, when administered jointly, 5-hydroxytryptophan and opiates may act to offset each other's most characteristic side effect.

To explore the practical utility of these proposals, we intend to test the impact of the joint administration of DLPA, 5-hydroxytryptophan, and Hypericum extract (St John's wort) in the management of chronic pain; inclusion of tyrosine in this regimen will also be considered. (Hypericum is noted for its excellent tolerance, and is widely prescribed in Europe as a treatment for mild depression; its prime active component appears to be hyperforin, which functions as a serotonin reuptake inhibitor in nanomolar concentrations.) (65–69). Provided that the dose of 5-hydroxytryptophan is not excessive, we anticipate that this regimen will be well tolerated. This regimen has the further advantage that, should it prove effective, it could be marketed in the US as a 'supplement', without the necessity of an expensive drug approval process. Although chiefly construed as an adjuvant to treatments that activate the EAS, this regimen may possibly have direct clinical utility in fibromyalgia, a hyperalgesic syndrome of obscure etiology that is reported to respond to serotonergic measures (70–73).

REFERENCES

1. Portenoy R. K., Foley K. M. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain* 1986; **25**: 171–186.
2. American Academy of Pain Medicine, American Pain Society. The use of opioids for the treatment of chronic pain – a consensus statement. *Pain Res Management* 1997; **2**: 126.
3. Fischer E., Heller B., Nachon M., Spatz H. Therapy of depression by phenylalanine. *Arzneim-Forsch* 1975; **25**: 132.
4. Spatz H., Heller B., Nachon M., Fischer E. Effects of D-phenylalanine in clinical picture and phenetylaminuria in depression. *Biol Psychiatry* 1975; **10**: 235–238.
5. Beckmann H., Strauss A., Ludolph E. DL-phenylalanine in depressed patients: an open study. *J Neurol Transm* 1977; **41**: 123–134.
6. Beckmann H., Athen D., Olteanu M., Zimmer R. DL-phenylalanine versus imipramine: a double-blind controlled study. *Arch Psychiat Nervenkr* 1979; **227**: 49–58.
7. Ehrenpreis S. Analgesic properties of enkephalinase inhibitors: animal and human studies. *Prog Clin Biol Res* 1985; **192**: 363–370.
8. Ehrenpreis S. Pharmacology of enkephalinase inhibitors: animal and human studies. *Acupunct Electrother Res* 1985; **10**: 203–208.
9. Nurmikko T., Pertovaara A., Pontinen P. J. Attenuation of tourniquet-induced pain in man by D-phenylalanine, a putative inhibitor of enkephalin degradation. *Acupunct Electrother Res* 1987; **12**: 185–191.
10. Ninomiya Y., Kawamura H., Nomura T. et al. Analgesic effects of D-amino acids in four inbred strains of mice. *Comp Biochem Physiol C* 1990; **97**: 341–343.
11. Panocka I., Sadowski B. Potentiation of swim analgesia by D-amino acids in mice is genotype dependent. *Pharmacol Biochem Behav* 1990; **37**: 593–596.
12. Halpern L. M., Dong W. K. D-phenylalanine: a putative enkaphalinase inhibitor studied in a primate acute pain model. *Pain* 1986; **24**: 223–237.
13. Walsh N. E., Ramamurthy S., Schoenfeld L., Hoffman J. Analgesic effectiveness of D-phenylalanine in chronic pain patients. *Arch Phys Med Rehabil* 1986; **67**: 436–439.

14. Cheng R. S., Pomeranz B. A combined treatment of D-amino acids and electro-acupuncture produces a greater analgesia than either treatment alone; naloxone reverses these effects. *Pain* 1980; **8**: 231–236.
15. Kitade T., Minamikawa M., Nawata T. et al. An experimental study on the enhancing effects of phenylalanine on acupuncture analgesia. *Am J Chin Med* 1981; **9**: 243–248.
16. Kitade T., Odahara Y., Shinohara S. et al. Studies on the enhanced effect of acupuncture analgesia and acupuncture anesthesia by D-phenylalanine (first report) – effect on pain threshold and inhibition by naloxone. *Acupunct Electrother Res* 1988; **13**: 87–97.
17. Kitade T., Odahara Y., Shinohara S. et al. Studies on the enhanced effect of acupuncture analgesia and acupuncture anesthesia by D-phenylalanine (2nd report) – schedule of administration and clinical effects in low back pain and tooth extraction. *Acupunct Electrother Res* 1990; **15**: 121–135.
18. Kaliuzhnyi L. V., Kozlov AIu. Action of an enkephalinase blocker on the effect of acupuncture in acupuncture sensitive and resistant rabbits. *Biull Eksp Biol Med* 1991; **112**: 571–573.
19. Dove B., Morgenstern E., Gores E. The analgesic action of d-phenylalanine in combination with morphine or methadone. *Pharmazie* 1991; **46**: 875–877.
20. Mann J., Peselow E. D., Snyderman S., Gershon S. D-phenylalanine in endogenous depression. *Am J Psychiatry* 1980; **137**: 1611–1612.
21. Basbaum A. I., Fields H. L. Endogenous pain control mechanisms: review and hypothesis. *Ann Neurol* 1978; **4**: 451–462.
22. Basbaum A. I., Fields H. L. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. *Ann Rev Neurosci* 1984; **7**: 309–338.
23. Barbaro N. M., Hammond D. L., Fields H. L. Effects of intrathecally administered methysergide and yohimbine on microstimulation-produced antinociception in the rat. *Brain Res* 1985; **343**: 223–229.
24. Jones S. L., Gebhart G. F. Inhibition of spinal nociceptive transmission from the midbrain, pons and medulla in the rat: activation of descending inhibition by morphine, glutamate and electrical stimulation. *Brain Res* 1988; **460**: 281–296.
25. Budai D., Fields H. L. Endogenous opioid peptides acting at mu-opioid receptors in the dorsal horn contribute to mid-brain modulation of spinal nociceptive neurons. *J Neurophysiol* 1998; **79**: 677–687.
26. Liu X., Zhu B., Zhang S-X. Relationship between electroacupuncture analgesia and descending pain inhibitory mechanism of nucleus raphe magnus. *Pain* 1986; **24**: 383–396.
27. Ma Q-P., Zhou Y., Yu Y-X., Han J-S. Electroacupuncture accelerated the expression of c-fos protooncogene in serotonergic neurons of nucleus raphe dorsalis. *Intern J Neurosci* 1992; **67**: 111–117.
28. Skolnick M. H., Wilson O. B., Hamilton R. F. et al. Low current electrostimulation produces naloxone-reversible analgesia in rats. *Stereotact Funct Neurosurg* 1989; **53**: 125–140.
29. Malin D. H., Lake J. R., Hamilton R. F., Skolnick M. H. Augmented analgesic effects of enkephalinase inhibitors combined with transcranial electrostimulation. *Life Sci* 1989; **44**: 1371–1376.
30. Warner R., Hudson-Howard L., Johnston C., Skolnick M. Serotonin involvement in analgesia induced by transcranial electrostimulation. *Life Sci* 1990; **46**: 1131–1138.
31. Malin D. H., Lake J. R., Hamilton R. F., Skolnick M. H. Augmented analgesic effects of L-tryptophan combined with low current transcranial electrostimulation. *Life Sci* 1990; **47**: 263–267.
32. Melzack R., Wall P. D. Pain mechanisms: a new theory. *Science* 1965; **150**: 971–979.
33. Freeman T. B., Campbell J. N., Long D. M. Naloxone does not effect pain relief induced by electrical stimulation in man. *Pain* 1983; **17**: 189–195.
34. Lee K. H., Chung J. M., Willis W. D. Jr. Inhibition of primate spinothalamic tract cells by TENS. *J Neurosurg* 1985; **62**: 276–287.
35. Wang J. Q., Mao L., Han J. S. Comparison of the antinociceptive effects induced by electroacupuncture and transcutaneous electrical nerve stimulation in the rat. *Int J Neurosci* 1992; **65**: 117–129.
36. Lin J. G., Chen X. H., Han J. S. Antinociception produced by 2 and 5 KHz peripheral stimulation in the rat. *Int J Neurosci* 1992; **64**: 15–22.
37. Hansson P., Ekblom A., Thomsson M., Fjellner B. Influence of naloxone on relief of acute oro-facial pain by transcutaneous electrical nerve stimulation (TENS) or vibration. *Pain* 1986; **24**: 323–329.
38. Meng I. D., Manning B. H., Martin W. J., Fields H. L. An analgesia circuit activated by cannabinoids. *Nature* 1998; **395**: 381–383.
39. Sandyk R. L-tryptophan in neuropsychiatric disorders: a review. *Intern J Neurosci* 1992; **67**: 127–144.
40. Birdsall T. C. 5-Hydroxytryptophan: a clinically-effective serotonin precursor. *Altern Med Rev* 1998; **3**: 271–280.
41. Milner J. D., Wurtman R. J. Catecholamine synthesis: physiological coupling to precursor supply. *Biochem Pharm* 1986; **35**: 875–881.
42. Reche I., Ruiz-Gayo M., Fuentes J. A. Inhibition of opioid-degrading enzymes potentiates delta9-tetrahydrocannabinol-induced antinociception in mice. *Neuropharmacol* 1998; **37**: 215–222.
43. Gray A. M., Spencer P. S., Sewell R. D. The involvement of the opioidergic system in the antinoceceptive mechanism of action of antidepressant compounds. *Br J Pharmacol* 1998; **124**: 669–674.
44. Chipkin R. E., Latranyi M. B., Iorio L. C. Potentiation of stress-induced analgesia (SIA) by thiorphan and its block by naloxone. *Life Sci* 1982; **31**: 1189–1192.
45. Greenburg R., O'Keefe E. H. Thiorphan potentiation of stress-induced analgesia in the mouse. *Life Sci* 1982; **31**: 1185–1188.
46. Han C. S., Chou P. H., Lu C. C. et al. The role of central 5-hydroxytryptamine in acupuncture analgesia. *Sci Sin* 1979; **22**: 91–104.
47. Hosobuchi Y., Lamb S., Baskin D. Tryptophan loading may reverse tolerance to opiate analgesics in humans: a preliminary report. *Pain* 1980; **9**: 161–169.
48. Malec D. Central action of narcotic analgesics. VI. Further studies on the participation of serotonin in the action of analgesics. *Pol J Pharmacol Pharm* 1980; **32**: 665–672.
49. Cheng R. S., Pomeranz B. Monoaminergic mechanism of electroacupuncture analgesia. *Brain Res* 1981; **215**: 77–92.
50. Seltzer S., Stoch R., Marcus R., Jackson E. Alteration of human pain thresholds by nutritional manipulation and L-tryptophan supplementation. *Pain* 1982; **13**: 385–393.
51. Seltzer S., Dewart D., Pollack R. L., Jackson E. The effects of dietary tryptophan on chronic maxillofacial pain and experimental pain tolerance. *J Psychiatr Res* 1982; **17**: 181–186.
52. Shpeen S. E., Morse D. R., Furst M. L. The effect of tryptophan on postoperative endodontic pain. *Oral Surg Oral Med Oral Pathol* 1984; **58**: 446–449.
53. Abbott F. V., Young S. N. Effect of 5-hydroxytryptamine precursors on morphine analgesia in the formalin test. *Pharmacol Biochem Behav* 1988; **31**: 855–860.

54. Warner R., Hudson-Howard L., Johnston C., Skolnick M. Serotonin involvement in analgesia induced by transcranial electrostimulation. *Life Sci* 1990; **46**: 1131–1138.
55. Ceccherelli F., Diani M. M., Altafini L. et al. Postoperative pain treated by intravenous L-tryptophan: a double-blind study versus placebo in cholecystectomized patients. *Pain* 1991; **47**: 163–172.
56. Abbott F. V., Etienne P., Franklin K. B. et al. Acute tryptophan depletion blocks morphine analgesia in the cold-pressor test in humans. *Psychopharmacology* 1992; **108**: 60–66.
57. Larson A. A., Takemore A. E. Effect of fluoxetine hydrochloride (Lilly 110140), a specific inhibitor of serotonin uptake, on morphine analgesia and the development of tolerance. *Life Sci* 1977; **21**: 1807–1811.
58. Hynes M. D., Lochner M. A., Bemis K. G., Hymson D. L. Fluoxetine, a selective inhibitor of serotonin uptake, potentiates morphine analgesia without altering its discriminative stimulus properties or affinity for opioid receptors. *Life Sci* 1985; **36**: 2317–2323.
59. Bragin E. O., Batueva N. N., Vasilenko G. F. et al. Effect of amitriptyline on analgesia induced by acupuncture and inescapable painful electrodermal stimulation in the rat. *Farmakol Toksikol* 1989; **52**: 22–25.
60. Tura B., Tura S. M. The analgesic effect of tricyclic antidepressants. *Brain Res* 1990; **518**: 19–22.
61. Amelin A. V., Vasil'ev IuN, Ignatov IuD, Skoromets A. A. The combined use of acupuncture and antidepressants for managing the spondylogenic lumbosacral pain syndrome. *Farmakol Toksikol* 1991; **54**: 12–13.
62. Hull K. M., Tolland D. E., Maher T. J. L-Tyrosine potentiation of opioid-induced analgesia utilizing the hot-plate test. *J Pharmacol Exp Ther* 1994; **269**: 1190–1195.
63. Kawabata A., Kasamatsu K., Takagi H. L-tyrosine-induced antinociception in the mouse: involvement of central delta-opioid receptors and bulbo-spinal noradrenergic system. *Eur J Pharmacol* 1993; **233**: 255–260.
64. Jaffe B. M. Prostaglandins and serotonin:nonpeptide diarrheogenic hormones. *World J Surg* 1979; **3**: 565–578.
65. Miller A. L. St. John's Wort (hypericum perforatum): clinical effects on depression and other conditions. *Altern Med Rev* 1998; **3**: 18–26.
66. Perovic S., Muller W. E. Pharmacological profile of hypericum extract. Effect on serotonin uptake by postsynaptic receptors. *Arzneimittelforschung* 1995; **45**: 1145–1148.
67. Chatterjee S. S., Noldner M., Koch E., Erdelmeier C. Antidepressant activity of hypericum perforatum and hyperforin: the neglected possibility. *Pharmacopsychiatry* 1998; **31**(Suppl 1): 7–15.
68. Muller W. E., Singer A., Wonnemann M. et al. Hyperforin represents the neurotransmitter reuptake inhibiting constituent of hypericum extract. *Pharmacopsychiatry* 1998; **31**(Suppl 1): 16–21.
69. Chatterjee S. S., Bhattacharya S. K., Wonnemann M. et al. Hyperforin as a possible antidepressant component of hypericum extracts. *Life Sci* 1998; **63**: 499–510.
70. Carus I., Sarzi Puttini P., Cazzola M., Azzolini V. Double-blind study of 5-hydroxy-tryptophan versus placebo in the treatment of primary fibromyalgia syndrome. *J Int Med Res* 1990; **18**: 201–209.
71. Puttini P. S., Caruso I. Primary fibromyalgia syndrome and 5-hydroxyl-L-tryptophan: a 90-day open study. *J Int Med Res* 1992; **20**: 182–189.
72. Nicolodi M., Sicuteri F. Fibromyalgia and migraine, two faces of the same mechanism. Serotonin as the common clue for pathogenesis and therapy. *Adv Exp Med Biol* 1996; **398**: 373–379.
73. Bennett R. Fibromyalgia, chronic fatigue syndrome, and myofascial pain. *Curr Opin Rheumatol* 1998; **10**: 95–103.