Endorphins and Pain Perception in Silent Myocardial Ischemia

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Evidence suggests that endogenous opioids, particularly the β-endorphins and met-enkephalins, are closely involved in stress-induced analgesia and nociceptive pain control. Numerous investigations have been conducted to evaluate the role of opioids in silent vs symptomatic myocardial disease. There is good evidence to suggest that patients with asymptomatic ischemia have defective pain perception compared with those with angina; however, the precise role of the endorphin and enkephalin systems in this phenomenon remains to be elucidated. Possible sources for disparate study results include variation in patient populations, insensitive or improperly timed assay techniques, and differences in amount of ischemia.

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The endogenous opioids are derived from larger precursor molecules. For example, pro-enkephalin A gives rise to several molecules of methionine (met)-enkephalin and 1 molecule of leucine-enkephalin. Dynorphin is created by cleavage of pro-dynorphin. Pro-opiomelanocortin is the progenitor of β-endorphin, the most potent endogenous opioid peptide yet discovered. Endogenous opioids are pharmacologically similar to, and show cross-tolerance with, morphine. Their action is reversed by naloxone.

Enkephalins, abundant throughout the central nervous system, are also found in the gut, sympathetic nervous system and adrenal medullary chromaffin cells. Dynorphin peptides are located similarly but are released from different cells; their function has not been clearly delineated. Beta-endorphins are produced in cells located in the arcuate nucleus of the hypothalamus and the pituitary. Each of these types of opioid peptides are contained in structures closely involved with nociceptive pain control.

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Circulating endorphins are probably important in stress-induced analgesia. For instance, hypophysectomy or adrenomedullectomy in rats blunts opioid-dependent analgesia.[1,2] A recent study by Carr suggests that reflux of β-endorphins from blood into cerebrospinal fluid (CSF) contributes to an increase in CSF endorphin levels.[3] Endorphin levels are increased in response to exercise, in a magnitude that is directly related to the intensity of effort and degree of training. A case in point is the well-documented rise in plasma β-endorphin and met-enkephalin levels that occurs after running.

The evidence that psychological stressors influence circulating endorphin levels in humans is inconclusive. Reports have been published associating increased β-endorphin levels with the stress of an impending examination, and increased opioid activity has been observed in subjects engaged in cognitive and attentive tasks. In these studies, the amount of subjective stress experienced was closely related to opioid levels, suggesting a direct relation between endorphin response, psychophysiologic arousal and personality variables.[4]

Pain Perception in Patients with Asymptomatic Ischemia

The conflicting results of various investigations obscure the precise role of endorphins in the pathogenesis of silent myocardial ischemia.

In 1983, Droste and Roskamm[5] studied pain thresholds and tolerance in 20 patients with asymptomatic

TABLE I Summary of Studies Investigating the Effect of Naloxone on Pain Response in Patients with Myocardial Ischemia

	Droste & Roskamm 1984[5]	Ellestad & Kuan 1984[8]	Van Rijn & Rabkin 1986[7]
Subject	30 asymptomatic and 30 symptomatic on exercise testing	10 without angina; 7 = type I, 3 = type II (post-MI)	5 with exercise-induced angina
Type test	Cold pressor Electric skin stimulation Ischemic forearm tourniquet test Repeat testing after naloxone and placebo in 10 asymptomatics	2 multistage treadmill tests in 1 week, with naloxone injected before the 2nd test	3 multistage treadmill tests in 3 successive weeks: control; naloxone & placebo double-blind
Naloxone	2 mg before pain tests	2 mg before 2nd test	2 mg, 5 min before 2nd or 3rd test
Results	Threshold & tolerance levels slightly decreased after naloxone (forearm pain only)	No angina in any subject, with or without naloxone	Angina significantly earlier after naloxone, compared with placebo

MI = myocardial infarction.

ischemia and 22 patients with reproducible angina. All patients with silent myocardial ischemia had a higher threshold for electrical and forearm ischemic pain and a higher tolerance for cold pressor and forearm ischemic pain than those with some angina. The responses of the 42 subjects on the Freiberger Personality Inventory Test elicited different psychological profiles for the 2 groups, which the investigators believed might contribute to discrepant pain thresholds. In 1984, these same investigators used the same experimental measures to test pain response in 30 asymptomatic and 30 anginal patients with myocardial ischemia, and again found higher thresholds and tolerance levels for the aforementioned stressors in the asymptomatic group. To evaluate the role of endogenous opioids in this pain perception, 10 asymptomatic patients were given 2 mg of naloxone. Threshold and tolerance levels for forearm ischemic pain were significantly decreased and were no longer substantially different from those of angina patients. In fact, 2 of the 10 patients had chest pain after naloxone administration.[6] These results suggest—although they do not prove—that the lack of symptoms in patients with silent myocardial ischemia is due to a generalized hyposensitivity to pain, and that higher levels of pain tolerance might be mediated by endorphins.

Data concerning the effects of opioid antagonists on the perception of myocardial ischemia are conflicting (Table I). Van Rijn and Rabkin[7] reported that administration of 2 mg of naloxone resulted in the earlier appearance of chest pain during treadmill testing in 6 patients with exercise-induced angina. Ellestad and Kuan[8] and Cohn et al,[9] using a similar dose of naloxone, failed to precipitate angina in patients with silent ischemia during exercise testing. Furthermore, the investigators could not confirm that naloxone influenced the pain threshold in patients with reproducible effort-induced angina.

From these results, it is certainly possible that endorphins modify pain perception in patients with and without silent ischemia, and that other factors are responsible for the differences in pain sensitivity. Because the mechanism responsible for painless ischemia may be different in some patients than in others, conflicting results in studies evaluating the effects of naloxone may be due to patient selection. Also, the dose of naloxone used in these studies may not be adequate enough to block the relevant receptor sites.

In brief, there is good evidence to suggest that patients with painless myocardial ischemia have defective pain perception. In some cases, this defect is influenced by naloxone.

Beta-Endorphin Activity in Patients with Angina Versus Silent Ischemia: Study Design and Results

To test the hypothesis that endorphin secretion during exercise is related to the perception of chest pain in patients with coronary disease and angina, we measured plasma β-endorphin levels by radioimmunoassay before and after exercise in 25 patients with ischemia manifested by angina, a positive treadmill test result, and/or a positive result during exercise radionuclide study.

All patients rested at baseline for 1 to 2 hours. A supine radionuclide study was performed and blood obtained for β-endorphin analysis. Additional samples were obtained for endorphin analysis immediately after the patient performed a symptom-limited supine exercise test.

Overall results showed that the mean postexercise level of plasma β-endorphin—6.5 pmol/liter—was significantly higher than the baseline level of 4.92 pmol/liter. Fifteen patients had chest pain during exercise and 10 remained asymptomatic despite electrocardio-

TABLE II Correlation Between Plasma Endorphin Levels and Various Physiologic Parameters. Poststress Endorphin Levels Show a Positive Correlation with Time to Onset of Angina and a Negative Association with Occurrence and Duration of Angina

	Rest Endorphin	Poststress Endorphin	Difference
Angina	−0.24 (0.24)	−0.41* (0.04)	−0.24 (0.25)
Duration of angina	−0.35 (0.08)	−0.39* (0.05)	−0.15 (0.48)
Time to onset of angina	0.29 (0.16)	0.43* (0.03)	0.22 (0.28)
Maximal ST depression	−0.04 (0.86)	0.05 (0.81)	0.05 (0.81)
Time to ST depression (1 mm)	0.05 (0.81)	−0.08 (0.71)	−0.11 (0.62)
Rest ejection fraction (%)	0.29 (0.17)	0.48* (0.02)	0.28 (0.18)
Stress ejection fraction (%)	0.15 (0.48)	0.17 (0.42)	0.03 (0.88)
Peak work load (kpm/min)	−0.08 (0.69)	0.08 (0.71)	0.14 (0.50)

* $p \leq 0.05$.
Numbers in parentheses are p values.

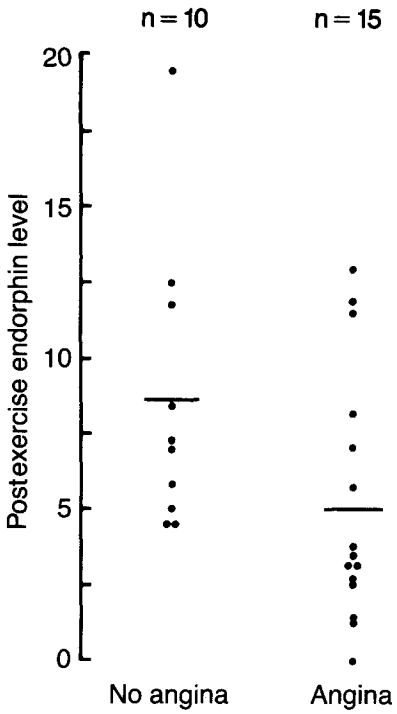

FIGURE 1. Postexercise plasma β-endorphin levels in patients who did not have angina vs those who did. The mean value in patients with angina is approximately 41% lower than it is in patients without angina despite considerable overlap.

TABLE III Summary of Studies Investigating the Plasma β-Endorphin Response in Patients with Myocardial Ischemia

	Glazier et al 1986[11]	Weidinger et al 1986[12]	Heller et al 1987[13]	Sheps et al 1987[10]
Subjects	6 asymptomatic 5 symptomatic	1 type I 4 type II 5 type III (2 post–MI) 6 normals	On exercise test: 10 anginal 12 angina-free (4 type I; 8 type II) 10 normals	25 anginal on exercise (22 in daily life; 16 post–MI)
Type test	Cold pressor Electric skin stimulation Ischemic forearm tourniquet test	2 symptom-limited upright bicycle tests, the 2nd after naxolone	Treadmill after 1 hour relaxation	Supine bicycle exercise
Blood	Baseline & at tolerance time for forearm ischemic pain	Rest, peak exercise, & 5 mins after recovery	Before, every 3 min during, & 10, 20 & 30 min after exercise	Immediately before & after exercise
Radioimmunoassay	Per Clement Jones et al and Jeffcoate et al*	New England Nuclear Kit	Immuno-nuclear Corp.	Immuno-nuclear Corp.
Results	β-endorphin levels similar during basal state & induction of forearm pain in both groups	Slight but no significant increase in β-endorphin levels postexercise in CAD pts and controls; no angina	β-endorphin levels elevated postexercise in all groups	Poststress β-endorphin levels significantly lower in anginal pts than in asymptomatic pts; positive correlation w/time to onset

CAD = coronary artery disease; MI = myocardial infarction; w/ = with.

* Clement-Jones V, Lowry PJ, Rees LH, Besser GM. Metenkephalin circulates in human plasma. Nature 1980; 283:295–297. Jeffcoate WJ, Rees LH, Lowry PH, Hope J, Besser GM. β-lipotrophin in human plasma and cerebrospinal fluid: radioimmunoassay evidence for γ-lipotrophin and β-endorphin. J Endocrinol 1978; 77:27P–28P.

graphic evidence of ischemia lasting an average of 3 minutes. A comparison of β-endorphin levels in those who had angina vs those who did not showed that β-endorphin levels were 41% lower in the angina group (Fig. 1). Postexercise β-endorphin levels were negatively correlated with occurrence and duration of angina and positively associated with time to onset of angina. No relation was found between endorphin levels and maximal heart rate × blood pressure product, work load, total work performed or ST-segment depression (Table II).[10]

Results of Other Investigations

Several other studies have measured plasma β-endorphin levels as a means of examining pain mechanisms in patients with coronary disease (Table III). Glazier et al[11] compared pain perception in patients with silent myocardial ischemia and chronic stable angina. Patients were divided into 2 groups, according to whether painless (group A) or painful ischemia (group B) was predominant. Patients in group A had episodes of ST-segment depression that were greater than 2 mm, occurring during 2 or more exercise tests; over 90% of episodes during repeat Holter monitoring were painless. Those in group B had more than 50% of episodes of ST depression occurring with pain during repeat Holter. Study participants were subjected to such stressors as cold pressor tests, ischemic forearm tourniquet tests and electrical stimulation.

Group A had a significantly higher threshold and tolerance for all stressors. The investigators compared β-endorphin, met-enkephalin, noradrenalin and adrenalin levels at basal state and during pain tolerance between both groups. There were no significant differences, and no correlation was obtained between these levels and pain characteristics. However, the investigators did not measure endorphin levels or any other hormones during spontaneous or exercise-induced ischemia.[11]

Weidinger et al[12] studied endorphin levels in 10 patients, 5 of whom were asymptomatic and 5 of whom had a mixed classification of type III chest pain. Patients performed 2 symptom-limited, submaximal bicycle exercise tests. Blood samples were obtained at rest, peak exercise and 5 minutes after recovery. Five minutes before the second test 1.2 mg of naloxone was injected. None of the study participants had angina, with or without naloxone, and patients in both groups had slightly higher β-endorphin levels during exercise.[12].

Heller et al[13] evaluated 3 groups of patients: normal control subjects, those with coronary disease and no history of angina, and those with coronary disease and exercise-induced angina. Patients exercised submaximally to the onset of angina. Blood samples were obtained immediately before exercise, every 3 minutes during exercise, and 10, 20 and 30 minutes after exercise. The groups demonstrated no differences in their β-endorphin response to exercise, all having a significant increase within 10 minutes after exercising.[13]

Conclusions

Differences in these study results could be due, in part, to discrepant or insensitive radioimmunoassay techniques, since some assays exhibit significant cross-reactivity to nonopioid peptides. Variation in patient populations—particularly in psychological profile, amount of baseline ischemia or degree of physical conditioning—is another possible source for inconsistency. The time of day that studies were performed and blood samples were obtained is also important, because β-endorphin levels are known to peak during morning hours[14]—the same time when ischemic activity is highest.[15]

It is hoped that further investigation will produce more consistent results and will clarify the role of endorphins in silent ischemia. Additional knowledge about defective pain perception in patients with asymptomatic coronary disease may hold the key to early and more effective diagnosis.

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