The Relationship Between Repressive and Defensive Coping Styles and Monocyte, Eosinophile, and Serum Glucose Levels: Support for the Opiod Peptide Hypothesis of Repression

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The opioid peptide hypothesis of repression (1) predicts that repressive coping is associated with increased functional endorphin levels in the brain, which can result in decreased immunocompetence and hyperglycemia. In a random sample of 312 patients seen at a Yale Medical School outpatient clinic, significant main effects of coping style were found for monocyte and eosinophile counts, serum glucose levels, and self-reports of medication allergies. Specifically, repressive and defensive high-anxious patients demonstrated significantly decreased monocyte counts. In addition, repressive coping was associated with elevated eosinophile counts, serum glucose levels, and self-reported reactions to medications. This behavioral, immunologic, and endocrine profile is consistent with the opioid peptide hypothesis, which provides an integrative framework for relating the attenuated emotional experience of pain and distress characteristic of repressive coping with reduced resistance to infectious and neoplastic disease.

Individual differences in coping styles have been associated with differences in response and adjustment to pain and illness, and to short- and long-term treatment (1–3). The repressive tendency represents a coping strategy against threatening information characterized by a general orientation away from threat and a denial or minimization of distress and negative emotions (4–5). Numerous studies have demonstrated, across varied conditions of challenge, that repressors typically report significantly lower levels of negative emotions (anxiety, tension, anger, depression) (5–7), somatic symptoms (8), and affective pain appreciation (9); and greater tolerance of nociceptive stimulation (9–10) compared with nonrepressive populations.

Repressive coping has been associated with impaired immune function in the form of increased risk and worsened clinical course of neoplastic disease (11, 12, 15, see 13, 14 for reviews). The inability to express emotion, particularly the denial or suppression of anger, has been found to be a strong predictor of cancer incidence and course (11, 16, 17). On the other hand, length of survival has been found to be positively correlated with expression of nonacceptance of cancer, general discontentment (18), "fighting spirit," and denial (19). Conversely, cancer patients employing passive coping styles (i.e., stoic acceptance or helplessness) have shown shorter survival lengths (19).

Jamner and Schwartz (9) have proposed

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an endogenous opioid modulator model to account for the accumulating experimental and clinical observations related to repressive coping. Specifically, the opioid peptide hypothesis postulates that the repressive coping style is associated with greater central endogenous opioid system activity. The attenuated experiences of distress, affective pain appreciation and somatic symptomatology and the accentuated report of positive emotions documented among repressors are consistent with the observed actions of centrally active opioid peptides (20, 21).

The postulated relationship between repressive coping and functional levels of endogenous opioid peptides is supported by a number of studies that have implicated endorphinergic systems in the modulation of human mood and well-being. The administration of opioid antagonists such as naloxone has been shown to induce dose-dependent increases in the subjective experience of tension, anxiety, anger, and hostility (22, 23); decreased ratings of joy and euphoria (23, 24); increases in the affective unpleasantness of experienced pain (25); and increases in the recognition of effort-induced pain (26). Greater functional levels of endogenous opioids among repressors are further suggested by research that has shown naloxone-related hyperalgesia to be elicited reliably only among individuals identified as pain-insensitive (27–29) or those who demonstrated positive response sets (30–32). Unfortunately these studies did not assess repressive coping in their samples, but it seems reasonable that the "pain-insensitive" individuals may be repressors and therefore have higher basal levels of endogenous opioids.

The observed relationships between repressive coping and cancer risk are also consistent with the opioid modulator theory. Recent investigations of the effects of endogenous opioids and other neuropeptides on immune mechanisms suggest that they may contribute significantly to in vivo immunoregulatory functions (33–37). In vitro natural killer (NK) cytolytic and macrophage-mediated tumorcidal activities have been shown to vary as a function or either β-endorphin (β-ENDO), α-endorphin (α-ENDO), Met-enkaphalin (ME), or adrenocorticotropic hormone (ACTH) administration (34, 37, 38). In vivo investigations have shown exposure to a diverse number of stressors to be related to increases in plasma and central levels of endogenous opioids (23, 36, 39). Immunosuppression associated with exposure to stress has been demonstrated to involve endogenous opioid mediation as evidenced by studies showing naloxone reversal of endotoxin-induced depression of circulating leukocytes and platelet levels (40), and decreased resistance to tumor challenge associated with intracerebroventricularly administered morphine (35). In the present investigation, we sought to test predictions derived from the opioid peptide hypothesis of repression by determining whether patients identified as repressors would manifest an endocrine and hematologic profile consistent with greater functional levels of brain endorphins. Repressive patients were predicted to demonstrate a reduction in endogenous opioid-related immune competence (i.e., reduced monocyte counts) as well as other endocrine responses related to higher brain endorphin levels (i.e., hyperglycemia).

METHODS

The medical records of 312 patients who presented themselves during the past 5 years to the Yale Be-

havioral Medicine Clinic, an outpatient service that evaluates and treats mostly stress-related disorders, were randomly selected and reviewed. All patients who present themselves at the clinic receive an initial psychological assessment and routine blood and urine tests prior to being examined by a physician. The patients were classified as repressive (REP; n = 79), defensive high-anxious (DEF: n = 69), true high-anxious (HA; n = 124), and true low-anxious (LA; n = 40) on the basis of their scores on the Marlowe–Crowne Social Desirability (MC) and Taylor Manifest Anxiety (Bendig Form; MAS) scales, which are administered as part of the initial psychological assessment. REP was defined as those with MAS scores less than 9 and MC scores of 17 or greater; LA, as MAS less than 9 and MC less than 17; DEF, as MAS of 9 or greater and MC of 17 or greater; HA, as MAS of 9 or greater and MC below 17. Blood samples were drawn between 2:00 and 4:30 PM on the day of the MAS and MC assessment and were analyzed (thyroid indices, manual CBC, and differential) at Yale–New Haven Hospital's hematology laboratory using standard procedures.[1] Medical histories, including self-reports of poor response including allergies to medications, were also obtained for all patients.

The populations described in this study were heterogeneous with respect to their presenting problems and prescribed medication use. Table 1 presents the means and standard deviations of patients' age, percent overweight,[2] and gender distributions for each group. The four groups were not found to differ with respect to age, percent overweight, or gender composition.

RESULTS

The findings of the study are presented in Figure 1a–c. Analyses of variance revealed significant main effects of coping style for monocyte count [$F(3,292) = 9.90$, $p < 0.001$], eosinophile count [$F(3,290) = 3.82$, $p < 0.01$], serum glucose levels [$F(3,308) = 3.07$, $p < 0.03$], and self-report of medication reactions including drug allergies [$F(3,336) = 5.68$, $p < 0.001$].

Tukey's HSD multiple-comparison procedure ($p = 0.05$) was used in all group comparisons. Analyses revealed that both REP and DEF patients demonstrated significantly reduced monocyte counts com-

[1]CBC differentials were derived using manual inspection and counting techniques by trained laboratory personnel.

[2]Percent overweight was defined as the actual/ideal weight ratio and expressed as a percentage. Patients' ideal weights were determined from weight/height actuarial tables (Metropolitan Life, 1983).

TABLE 1. Mean Age, Percent Overweight, and Gender Composition as a Function of Coping Style

Variable	Coping Style			
	REP[a]	DEF[b]	HA[c]	LA[d]
N	79	69	124	40
Age (years)	39 (14.1)[e]	40 (14.6)	37 (13.9)	38 (13.1)
Percent overweight	10 (26.5)	11 (22.1)	6 (21.3)	9 (33.0)
Gender composition				
Male	27	23	52	14
Female	52	46	72	26

[a]REP, repressive.
[b]DEF, defensive high-anxious.
[c]HA, true high-anxious
[d]LA, true low-anxious.
[e]Numbers in parentheses are standard deviations.

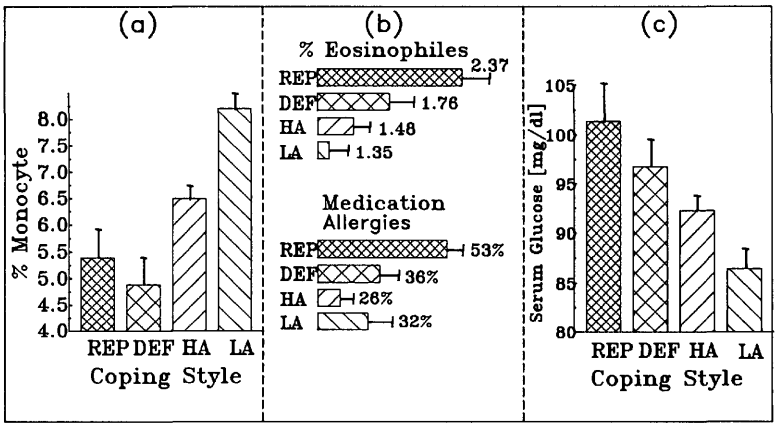

Fig. 1. (a) Mean monocyte count (per 100 leukocytes) as a function of REP, DEF, HA, and LA, coping styles. (b) Mean eosinophile count (per 100 leukocytes) and group percent of patients reporting allergies to medication as a function of coping style. (c) Mean serum glucose levels (mg/dl) for REP, DEF, HA, and LA groups.

pared with LA patients, and DEF displayed significantly lower monocyte levels than HA patients (see Fig. 1a.). REP patients also demonstrated significantly higher eosinophile counts than both LA and HA groups and reported significantly more medication reactions than all other groups (see Fig. 1b). A significant Allergy × Gender interaction was observed, with female patients reporting significantly greater medication reactions than male patients [$F(1,336) = 4.67, p < 0.03$]. The REP group also manifested significantly higher serum glucose levels than LA patients (see Fig. 1c.). The ANOVAs revealed no other main effects or interactions for either percent overweight or gender for any of these measures.

An analysis of patients' opiate histories (i.e., regular use vs. poor response) revealed a significant Copy × Opiate Response interaction (Fisher's Exact = 7.04, 1 *df*, $p < 0.005$). As shown in Table 2, REP and DEF (high MC) patients reported a lower frequency of regular opiate use (e.g., morphine, demorol, codeine) and a greater number of allergic-type reactions (e.g., hives, itching, nausea) related to their use of opiates than did HA and LA (low MC)

TABLE 2. Reported Incidences of Poor Response to or Regular Use of Opiates as a Function of Coping Style[a]

	Marlowe–Crowne	
	High[b]	Low[c]
Poor response	17	8
Regular use	4	14

[a]Fisher's Exact = 7.04, 1 *df*, $p < 0.005$.
[b]High MC, repressors and defensive high-anxious groups.
[c]Low MC, true high- and low-anxious groups.

patients who manifested the reverse pattern.

DISCUSSION

The results of this study extend earlier research documenting the influence of coping styles on hypothalamo–pituitary–adrenal phasic response to challenge (41–43) by demonstrating that individual differences in coping styles are related to basal differences in these systems as well. The hematologic and endocrine profile manifested by repressive patients is consistent with the hypothesis that repressive coping may be mediated by greater levels of brain β-endorphin.

It is noteworthy, however, that the defensive coping strategy was associated with the lowest monocyte levels. While the defensive high-anxious group showed the lowest levels of monocytes, the true high-anxious group failed to show a reduced monocyte count, clearly differentiating it from the repressive and defensive high-anxious groups.

The defensive high-anxious group may represent repressors (high endogenous opiates) whose coping mechanisms are failing and may have become ineffective. The "failed repressor" interpretation (i.e., defensive high-anxious coping) leads to the hypothesis that in addition to greater central endogenous opioid levels, greater levels of corticosteroids and/or catecholamines should also be present in these subjects. Support for this argument includes the results of a study investigating the effect of coping styles on neuroendocrine responses to a stressful interview among bereaved spouses (44). In that study, defensive high-anxious subjects were found to score significantly higher on an index of cortisol activity (combined urine and serum measures) than true high-anxious subjects, while repressors and true high- and low-anxious subjects failed to be differentiated on measures of cortisol activity.

Since it is known that both endogenous opiates and corticosteroids modulate immune function, it follows that increased levels of corticosteroids in the presence of increased levels of endogenous opiates could have additive or synergistic effects to further reduce immunocompetence as indicated by greater reductions in monocytes. The combination of increased endogenous opiates in the presence of increased corticosteroids could explain the reported interaction of greater social desirability with heightened distress as a predictor of worsened medical outcome in malignant melanoma (12).

The elevated serum glucose levels displayed by REP patients coincide with research demonstrating β-endorphin to be a potent hyperglycemic stimulus when delivered intracerebrally (45), and the reduction of stress- and endotoxin-induced hyperglycemia by centrally active but not peripherally active opiate antagonists (4 6, 47).

The hyperglycemic effect of CNS-administered and β-endorphin has been related to greater central autonomic outflow resulting in increased secretion of circulatory catecholamines (45, 48, 49). The strong positive relationship between plasma glucose and plasma epinephrine responses to increasing doses of intracisternally administered β-endorphin (49) suggests a common mechanism that integrates both the heightened levels of cardiovascular responsivity (5, 6) and elevated serum glucose levels observed among repressors.

While the documented effects of opioid peptides on basal levels of peripheral leukocytes and the relationship between cir-

culating leukocytes and resistance to neoplasia are less well delineated, the lower monocyte and elevated eosinophile counts shown by repressors in this study are consistent with clinical research suggesting that repression is associated with reduced natural resistance to neoplastic disease (11, 16).

Reduced monocyte counts have also been shown to predict increased susceptibility to infection among clinical populations (50) and reduced "T" lymphocyte blastogenic capability in healthy normals (51). The important role monocytes and macrophages (mature monocytes) play in host resistance against infection and neoplasia (52–54) makes the magnitude of the reduction in monocyte counts in repressor and defensive high-anxious patients particularly interesting.

Caution is needed, however, in drawing clinical inferences from our results until additional studies are conducted that relate specific measurements of immune function to clinical outcome. We are currently engaged in a follow-up study of our patient population to determine the relationship between coping styles, monocyte levels, and the subsequent incidence of disease.

Although glucocorticoid and catecholamine mechanisms have also been hypothesized to be mediators of immunoincompetence, serum corticosteroid levels have been found not to correlate with changes in stress-induced immunosuppression of natural resistance that was later reversed by naltrexone administration (32). The association between glucocorticoids and impaired immune function may be due, in part, to their shared relationship with endogenous opioids. Hypothalamic corticotropin releasing factor (CRF) has been shown to control both β-endorphin and glucocorticoid release (55). ACTH, which acts to stimulate adrenalcorticosteroid production, is coproduced along with β-endorphin. The inhibitory effects of glucocorticoids on β-endorphin production appear to be limited to pituitary β-endorphin release and have been shown not to affect brain or CSF β-endorphin levels (56). Given the tight neuroendocrine feedback loop between endogenous opioids and glucocorticoids, endorphinergic immunoregulation might appear to involve glucocorticoids in instances where only the steroid activity is assessed. Experiments in which the concomitant effects of both endogenous opioids and glucocorticoids on immune function are monitored may be required to further understand the relative contributions of both systems.

The lower frequency of regular opiate use and the greater number of allergic-type reactions to opiates reported by repressive and defensive high-anxious patients are also consistent with an opioid-modulator hypothesis of coping. That is, if repressive and defensive coping are mediated by greater levels of brain β-endorphin, one would expect that the administration of additional opioids would be of less utility. The pattern of opiate response and use shown by our sample is consonant with research associating repressive coping with lower levels of drug and alcohol use (57). The extent to which the pattern displayed by repressive and defensive high-anxious patients is unique to opioid preparations or extends to all psychoactive substances (e.g., sedatives, antidepressants) was not assessed in the present study and represents an alternative explanation for the observed findings.

In summary, patients identified as repressors demonstrated significantly reduced monocyte counts compared with low-anxious patients, greater eosinophile

counts compared with true high- and low-anxious patients, and greater serum glucose levels compared with the true low-anxious group. In addition, defensive high-anxious copers showed reduced monocyte counts compared with true high-and-low-anxious patients.

These findings are consistent with the opioid peptide hypothesis of repression (9), which postulates that repression is associated with increased functional endorphin levels in the brain, which in turn may result in decreased immunocompetence and hyperglycemia. We further hypothesize that defensive high-anxious coping (failed repression) is associated with increased endogenous opiate levels as well as an activation of the corticosteroid system. We are currently examining the dose-dependent effects of opiate antagonists to test more directly the observations and speculations derived from this study and other research concerning the specific biologic mechanisms linking the endorphinergic and immunologic systems with styles of coping with stress.

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