Corticosterone suppresses mesenteric lymph node T cells by inhibiting p38/ERK pathway and promotes bacterial translocation after alcohol and burn injury

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Submitted 17 November 2004; accepted in final form 11 February 2005

Nearly one million burn injuries are reported every year in the United States (2). Strikingly, alcohol (EtOH) use before injury is apparent in nearly 50% of burn patients (8, 22, 35–38). Furthermore, findings from previous studies suggest that EtOH intoxication at the time of injury plays a significant role in postinjury pathogenesis (8, 35–38, 48). These studies showed that burn patients who sustained injury under the influence of EtOH had significantly longer hospital stays, are more susceptible to infection, and are more likely to die than burn patients who sustained similar burn injury but had not consumed EtOH before injury. The mechanism underlying EtOH-induced increase in postburn morbidity and mortality remains unknown. Findings from experimental studies have shown that acute EtOH intoxication before burn injury impairs delayed type hypersensitivity, produces a greater suppression of mitogen-induced splenic-lymphocyte proliferation, and enhances susceptibility to bacterial infection (10, 18–20, 30, 40). Recent studies from our laboratory (6, 29) have shown that acute EtOH intoxication before burn injury enhances bacterial translocation. The increase in bacterial translocation was accompanied with suppression of intestinal T cell function and increased intestinal permeability (6). Furthermore, our studies suggested a correlation between T cell suppression and a decrease in p38 and ERK1/2 activation (i.e., phosphorylation) in mesenteric lymph node (MLN) T cells after EtOH intoxication and burn injury (11). Our studies collectively suggest that diminished intestinal T cell function and increased intestinal permeability are likely to contribute to increased bacterial translocation after EtOH and burn injury (6, 11, 29). Bacterial translocation has been observed after burn injury in a number of previous studies (4, 7, 16, 23, 24, 27, 47). Furthermore, these studies support the concept that intestine-derived factors including bacteria and their products play significant roles in initiating/exacerbating multiple organ dysfunction in acutely injured patients as well as in patients with EtOH intoxication (5, 8, 15, 20, 32).

To further delineate the mechanism of suppressed T cell responses and increased bacterial translocation, we attempted to determine whether glucocorticoids play any role in these responses. Glucocorticoids are pleiotropic hormones with a wide spectrum of immunomodulatory and anti-inflammatory properties. (3, 8, 18, 21, 39, 49, 50). They function by binding to glucocorticoid receptor, which resides in an inactive form in the cytoplasm of target cells (3, 44, 49). Upon interaction with the hormone, this receptor is transported into the nucleus, where it binds to discrete nucleotide sequences to alter the expression of specific genes. In addition, glucocorticoids are also known to inhibit the activation of mitogen-activated protein kinase (MAPK) pathways (13, 28).

Several lines of evidence suggest that EtOH intoxication and burn injury independently activate the hypothalamic-pituitary-adrenal (HPA) axis (8, 21, 23, 27, 33, 38, 39, 50). Corticosterone (Cort), which is the glucocorticoid end product of the HPA axis in rodents, plays an important role in influencing the immune system. There is evidence that elevated levels of Cort...
suppress macrophage and T cell functions (1, 2, 21, 23, 42, 46, 49, 50). In contrast, other studies suggest adrenal insufficiency to be the cause of impaired host ability to clear infectious agents (8, 18, 38). Thus the role of Cort after acute injury remains controversial. Because both EtOH intoxication and burn injury result in HPA activation, we tested the hypothesis that EtOH intoxication before burn injury enhances Cort levels, which in turn inhibits MLN T cell proliferation and increases bacterial translocation. Metyrapone, a Cort synthesis inhibitor, was used to block endogenous Cort synthesis. This substance inhibits 11β-hydroxylase, an enzyme responsible for the conversion of deoxycorticosterone, the Cort precursor, to Cort in the adrenal cortex (3). After establishing the role of Cort in T cell suppression, we also examined whether Cort mediates the suppression of T cells by altering the activation of p38, ERK1/2, and/or JNK, members of the MAPK family.

MATERIAL AND METHODS

Animals and reagents. Male Sprague-Dawley rats weighing 225–250 g were obtained from Charles River Laboratories (Wilmington, MA). Nylon wool was obtained from Polyscience (Warrington, PA). Reagents for cell culture were obtained from Fisher Scientific (Atlanta, GA). We used antibodies to p38 protein (catalog no. 9712; NEN Biolabs, Beverly, MA), phospho-p38 (Thr180/Tyr182, catalog no. 9211; NEN Biolabs), ERK1/2 protein (catalog no. 9102; NEN Biolabs), and phospho-ERK1/2 (Thr202/Tyr204, catalog no. 9101; NEN Biolabs). For JNK measurements, we used antibodies to stress-activated protein kinase (SAPK)/JNK protein (catalog no. 9252; NEN Biolabs) and phospho-SAPK/JNK (Thr183/Tyr185, catalog no. 4671).

EtOH was measured using a RIA kit, Coat-A-Count, provided by Diagnostic Products (Los Angeles, CA). Anti-rat CD3 antibodies were purchased from Pharmingen (San Diego, CA). Reagents for the SDS-PAGE were obtained from Bio-Rad (Richmond, CA). Immobilon P membrane (polyvinylidene difluoride) was obtained from Millipore (Bedford, MA). Protein molecular weight markers were obtained from Invitrogen (Carlsbad, CA). Antibodies to p38 protein are expressed as absorbance.

Measurement of bacterial translocation. MLN homogenate was cultured separately on Tryptic soy agar plates. The agar plates were incubated for 24–48 h at 37°C for bacterial growth. Bacterial colony-forming units were counted. If the plates did not show any bacterial growth up to 48 h, they were considered negative for the presence of bacteria.

Statistical analysis. These data are presented as means ± SE and were analyzed using the ANOVA statistical program. A P value <0.05 between groups was considered statistically significant.
intoxication compared with sham rats receiving saline. MLN T cell proliferation was decreased by 50% on day 2 after burn injury alone compared with sham-injured rats gavaged with saline or EtOH. A more than 75% decrease in MLN T cell proliferation was observed in rats receiving a combined insult of EtOH intoxication and burn injury compared with sham-injured rats gavaged with EtOH or saline. Furthermore, the decrease in MLN T cell proliferation after the combined insult of EtOH intoxication and burn injury was found to be 25% more compared with burn-injured rats gavaged with saline. Treatment of rats with metyrapone attenuated the EtOH- and burn-mediated decrease in MLN T cell proliferation.

**T cell IL-2 production.** Similar to proliferation, T cell IL-2 production was also decreased by ~70% in rats receiving a combined insult of EtOH intoxication and burn injury compared with sham-injured rats, regardless of their EtOH intoxication, and by nearly 50% compared with burn-injured rats gavaged with saline (Fig. 2B). Treatment of rats with metyrapone significantly prevented the decrease in MLN IL-2 production after EtOH intoxication and burn injury.

**T cell p38, ERK1/2, and JNK phosphorylation.** The phosphorylation of p38, ERK1/2, and JNK in T cells with and without anti-CD3 stimulation is shown in Figs. 3, 4, and 5.

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**RESULTS**

**Circulatory levels of Cort.** As shown in Fig. 1A, a significant increase in circulatory levels of Cort was observed within 4 h after rats were gavaged with EtOH (194 ± 5 ng/ml) compared with rats gavaged with saline alone (85 ± 14 ng/ml). Cort levels were significantly elevated on day 1 (218 ± 27 ng/ml) and day 2 (200 ± 20 ng/ml) in burn-injured rats compared with sham-injured rats gavaged with saline (105 ± 11.5 ng/ml). There was no significant difference in Cort levels between rats receiving either EtOH intoxication (202 ± 38 ng/ml on day 1 and 169 ± 30 ng/ml on day 2) or burn injury alone. However, rats receiving a combined insult of EtOH intoxication and burn injury exhibited a significant elevation in Cort levels (315 ± 27 ng/ml on day 1 and 300 ± 24 ng/ml on day 2) compared with the levels observed after either EtOH intoxication or burn injury alone.

In another group of animals, rats were treated with the Cort synthesis inhibitor metyrapone at a dose of 25 mg/kg body wt at the time of injury and on day 1 after injury. Circulatory Cort levels were measured on day 2 after injury. Results as presented in Fig. 1B suggest that treatment of rats with metyrapone significantly lowered the levels of Cort after EtOH and burn injury. Similar treatment did not influence Cort levels in sham-injured rats.

**T cell proliferation.** As shown in Fig. 2A, there was no change in MLN T cell proliferation in rats receiving EtOH gavaged with saline (85 ± 14 ng/ml) compared with rats gavaged with EtOH (194 ± 5 ng/ml). However, rats receiving a combined insult of EtOH intoxication and burn injury exhibited a significant decrease in MLN T cell proliferation compared with sham rats receiving saline. Furthermore, the decrease in MLN T cell proliferation after the combined insult of EtOH intoxication and burn injury was found to be 25% more compared with burn-injured rats gavaged with saline. Treatment of rats with metyrapone attenuated the EtOH- and burn-mediated decrease in MLN T cell proliferation.

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**Fig. 1.** Plasma levels of corticosterone (Cort) in untreated rats (A) and in rats treated with the Cort synthesis inhibitor metyrapone (B) after ethanol (EtOH) and burn injury. Rats were killed at different time points after EtOH intoxication and burn injury, and blood Cort levels were measured (A). A separate group of experimental rats was injected intraperitoneally with the Cort inhibitor metyrapone (25 mg/kg) at the time of injury and on day 1 after injury. Rats were killed on day 2 after EtOH and burn injury, and blood Cort levels were measured (B). Values are means ± SE from at least 6 animals in each group. *P < 0.05 compared with sham rats gavaged with saline. #P < 0.05 compared with burn-injured rats gavaged with saline and sham rats gavaged with EtOH.

**Fig. 2.** Treatment of rats with the Cort inhibitor metyrapone prevented suppression of mesenteric lymph node (MLN) T cell proliferation (A) and IL-2 production (B) on day 2 after EtOH and burn injury. Metyrapone (25 mg/kg) was injected at the time of injury and on day 1 after injury. For proliferation, MLN T cells (5 × 10^5 cells/well) were cultured with anti-CD3 (1 μg/ml) for 46 h at 37°C, pulsed with [3H]thymidine (0.5 μCi/well), and incubated for an additional 6 h at 37°C. Incorporation of radiolabeled thymidine into cells was counted and expressed as dpm. IL-2 was measured in supernatants harvested 48 h after T cells (5 × 10^5 cells/well) were cultured with anti-CD3 (1 μg/ml). Values are means ± SE from 6 animals in each group. *P < 0.05 compared with sham-injured rats gavaged with either saline or EtOH. #P < 0.05 compared with burn rats gavaged with saline.
respective. In unstimulated T cells, there was no difference in the phosphorylation of p38 (Fig. 3A), ERK1/2 (Fig. 4A), and JNK (Fig. 5A) in T cells obtained from rats receiving a combined insult of EtOH intoxication and burn injury compared with sham rat T cells. The stimulation with anti-CD3 resulted in a significant increase in the phosphorylation of p38, ERK1/2, and JNK in T cells derived from control and experimental animals; however, anti-CD3-mediated p38 (Fig. 3) and ERK1/2 (Fig. 4) phosphorylation was significantly lower in T cells from rats receiving a combined insult of EtOH and burn injury compared with those derived from rats receiving burn injury alone without prior EtOH intoxication or from sham-injured rats. There was no significant difference in JNK protein expression and phosphorylation (Fig. 5, A–C) in T cells derived from rats receiving a combined insult of EtOH and burn injury compared with rats receiving either EtOH intoxication or burn injury alone.

In our results, we observed a tendency of a decrease in total p38 (Fig. 3, A and B) and ERK1/2 (Fig. 4, A and B) protein levels in T cells after a combined insult of EtOH intoxication and burn injury; however, this decrease in total p38 and ERK1/2 protein levels was not found to be significantly different from that observed after either EtOH intoxication or burn injury alone. Nonetheless, we normalized p38 and...

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**Figure 3.** p38 phosphorylation and protein expression in MLN T cells after EtOH and burn injury. On day 2 postinjury, MLN T cells were isolated (1 × 10⁷ cells/ml), stimulated with anti-CD3 (1 µg/ml) for 5 min, and lysed. Lysates were then analyzed for p38 phosphorylation (p-p38) and protein expression (A). Blots were reprobed for β-actin for equal protein loading in various lanes. p38 blots obtained from 6 animals were analyzed using densitometry, and densitometric values were pooled and are shown as means ± SE in B. In addition, densitometric values for phosphorylation were normalized to the total protein. Normalized values for phosphorylation are shown as means ± SE in C. *P < 0.05 compared with sham rats gavaged with either saline or EtOH. #P < 0.05 compared with burn rats gavaged with saline. ^P > 0.05 compared with sham rats gavaged with saline or EtOH and burn rats gavaged with saline.

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**Figure 4.** ERK1/2 phosphorylation and protein expression in MLN T cells after EtOH and burn injury. On day 2 postinjury, MLN T cells were isolated (1 × 10⁷ cells/ml), stimulated with anti-CD3 (1 µg/ml) for 5 min, and lysed. Lysates were then analyzed for ERK1/2 phosphorylation (p-ERK1/2) and protein expression (A). Blots were reprobed for β-actin for equal protein loading in various lanes. ERK1/2 blots obtained from 6 animals were analyzed using densitometry; densitometric values were pooled and are shown as means ± SE in B. In addition, densitometric values for phosphorylation were normalized to the total protein. Normalized values for phosphorylation are shown as means ± SE in C. *P < 0.05 compared with sham rats gavaged with either saline or EtOH. #P < 0.05 compared with burn rats gavaged with saline. ^P > 0.05 compared with sham rats gavaged with saline or EtOH and burn rats gavaged with saline.
ERK1/2 phosphorylation by calculating the ratio of phosphorylation to the total protein expression. The results obtained from these ratio analyses suggest a nearly 30% decrease in p38 (Fig. 3C) and ERK1/2 (Fig. 4C) phosphorylation in MLN T cells derived from rats receiving burn injury in the absence of EtOH intoxication compared with sham alone. A nearly 75% decrease in p38 and ERK1/2 phosphorylation was observed in MLN T cells obtained from rats receiving a combined insult EtOH intoxication compared with sham-injured rats regardless of their EtOH intoxication. The decrease in MLN T cell p38 and ERK1/2 phosphorylation after EtOH intoxication and burn injury was found to be ~45% more compared with burn-injured rats gavaged with saline. There was no difference in p38 (Fig. 3C) and ERK1/2 (Fig. 4C) phosphorylation in MLN T cells obtained from sham rats gavaged with EtOH compared with sham rats gavaged with saline.

In a subsequent experiment, a group of sham and EtOH plus burn-injured rats was treated with metyrapone. MLN p38 and ERK1/2 protein and phosphorylation were determined. In these experiments we did not measure JNK because no change was observed in JNK activity after EtOH and burn injury. Results as presented in Fig. 6 show that treatment of rats with metyrapone prevented the suppression in T cell p38 (A) and ERK1/2 (B) phosphorylation observed after EtOH and burn injury. No effect of similar treatment was observed on MLN T cells isolated from sham rats gavaged with EtOH compared with sham rats gavaged with saline.

**MLN T cell apoptosis.** As shown in Fig. 7, there was no difference in T cell apoptosis after a combined insult of EtOH intoxication and burn injury alone compared with either EtOH intoxication or burn injury alone. Furthermore, the treatment of animals with Cort inhibitor metyrapone did not affect T cell apoptosis in rats receiving a combined insult of EtOH intoxication and burn injury.

**Bacterial accumulation.** As shown in Fig. 8, there was no change in bacterial accumulation in MLN of sham-injured animals regardless of their EtOH exposure. However, an increase in bacterial accumulation was noted in MLN of rats receiving burn injury alone in the absence of EtOH intoxication. A severalfold increase in bacterial accumulation was observed in MLN of rats receiving a combined insult of EtOH intoxication and burn injury compared with either EtOH intoxication or burn injury alone. Treatment of rats with metyrapone did not influence bacterial accumulation in MLN of sham-injured rats; however, a similar treatment of experimental rats significantly prevented the increase in bacterial accumulation observed after EtOH and burn injury.

**DISCUSSION**

In this study, we observed a significant increase in Cort levels after a combined insult of EtOH intoxication and burn injury. This was accompanied with suppression of MLN T cell proliferation and IL-2 production. Treatment of rats with the Cort inhibitor metyrapone prevented the decrease in T cell proliferation and IL-2 production after EtOH and burn injury. The results also suggest that Cort is likely to mediate T cell suppression by inhibiting p38 and ERK1/2 phosphorylation. Furthermore, we found that the restoration of T cell function in metyrapone-treated animals prevented the increase in bacterial accumulation in MLN. These findings collectively suggest that EtOH intoxication preceding burn injury augments the release of Cort and diminishes MLN T cell function, resulting in bacterial multiplication and their accumulation in MLN.

Kawakami et al. (30) have shown that although acute EtOH intoxication does not elevate Cort levels, a similar dose of EtOH given before burn injury augments the serum Cort levels. Consistent with these studies, the present findings suggest that a combined insult of EtOH intoxication and burn injury heighten-
ens the releases of Cort, which in turn causes MLN T cell suppression. In contrast, Faunce et al. (18) have shown a somewhat protective role of glucocorticoids after a combined insult of EtOH intoxication and burn injury. These authors (18) observed that whereas the individual insult of EtOH intoxication or burn injury resulted in increased Cort levels, a combination of the two insults (i.e., EtOH intoxication and burn injury) caused a decrease in Cort levels. They also showed that treatment of animals with Cort prevented the splenic T cell suppression following EtOH and burn injury. Although in our study we did not observe T cell apoptosis after a combined insult of EtOH intoxication and burn injury, a role of Cort in increased apoptosis following burn injury was supported in a previous study by Nakanishi et al. (39), who showed that adrenalectomy or treatment of rats with RU486 prevented the burn-induced thymocyte apoptosis. Hawes et al. (23) showed that chronic elevation of Cort for 4 days after burn injury alone or burn injury superimposed with burn wound infection adversely affected body mass and lymphocyte numbers and was correlated with increased mortality. Similarly, elevation in Cort after chronic EtOH intoxication has also been suggested that Cort levels tightly control immune cell functions. Thus any change in Cort levels as low as reported by Faunce et al. (18) or as high as has been shown in many injury conditions (1, 21, 23, 27, 30, 33, 39, 42) is likely to affect the immune response.

In many previous studies, elevated levels of Cort were shown to suppress both macrophage and T cell functions, including IL-2 and IFN-γ production (3, 8, 38, 44). In addition, Cort is also known to cause apoptosis in T and B cells. Although in our study we did not observe T cell apoptosis after a combined insult of EtOH intoxication and burn injury, a role of Cort in increased apoptosis following burn injury was supported in a previous study by Nakanishi et al. (39), who showed that adrenalectomy or treatment of rats with RU486 prevented the burn-induced thymocyte apoptosis. Hawes et al. (23) showed that chronic elevation of Cort for 4 days after burn injury alone or burn injury superimposed with burn wound infection adversely affected body mass and lymphocyte numbers and was correlated with increased mortality. Similarly, elevation in Cort after chronic EtOH intoxication has also been
correlated with the loss of CD4+ and CD8+ cells from thymus, spleen, and intestinal lymphoid organs, MLN, and Peyer’s patches (8, 38, 42, 46). Although these findings collectively suggest that elevation of Cort can lead to apoptosis and thereby to T cell function deficits under those conditions, in our study apoptosis was not found to be a cause of decreased T cell proliferation and IL-2 production. Rather, our results indicate that inhibition of p38 and ERK1/2 may be a component of signaling cascade that plays a role in Cort-mediated T cell suppression after a combined insult of EtOH intoxication and burn injury.

In the absence of injury, stimulation of resting cells with mitogen, anti-CD3, or antigen results in the activation of P56lck and P59fyn, which phosphorylate Zap-70 (7, 9, 12, 17, 26). ZAP-70 then phosphorylates phospholipase C-γ (PLC-γ) to hydrolyze phosphatidylinositol 4,5-bisphosphate into 1,4,5-trisphosphate [Ins(1,4,5)P3] and diacylglycerol (DAG). Ins(1,4,5)P3 releases the release of Ca2+ from intracellular as well as extracellular stores. DAG, on the other hand, activates PKC, resulting in activation of MAPKs, including p38, ERK1/2, and JNK (17). MAPKs then relay information to the nucleus through another series of downstream signaling molecules, leading to T cell activation. The resultant activated T cells mitotically divide and produce IL-2, which upon release interacts with IL-2 receptor expressed on T cells, leading to proliferation and subsequent cytokine production. Although the role of JNK along with p38 and ERK1/2 has been suggested in T cell proliferation and IL-2 production (17), the present findings suggest that JNK may not be critical to T cell suppression in EtOH- and burn-injured rats, because there was no change in JNK activity after EtOH intoxication and burn injury. Thus the suppression in p38 and ERK1/2 is likely to play a major role in Cort-mediated suppression of T cell proliferation and IL-2 production after a combined insult of EtOH intoxication and burn injury. Previous studies from our laboratory and others have shown that T cell dysfunction during burn and sepsis is accompanied with alterations in P59fyn kinase activity, PKC, and Ca2+ signaling (7, 8, 9, 12, 25). Because the activation of P56lck and Ca2+ signaling precedes p38 and ERK1/2 activation, alterations in either of these pathways may potentially contribute to a suppression of p38 and ERK1/2 in cells in EtOH and burn injury. However, a more direct effect of Cort on p38 and ERK1/2 is not ruled out. Although the mechanism by which Cort suppresses p38 and ERK1/2 in T cells after EtOH and burn injury remains to be established, previous studies in other cells have shown that Cort upregulates MAPK phosphatase, which in turn leads to inhibition of p38 and ERK1/2 activity (13, 28). This in turn results in decreased T cell proliferation and IL-2 production.

Our results support the suggestion that Cort-mediated inhibition of T cell functions is likely to contribute to increased bacterial accumulation in MLN after EtOH intoxication and burn injury. Previous studies have shown that administration of dexamethasone in healthy animals impairs IgA synthesis and increases bacterial translocation (1). Furthermore, other reports have indicated that elevations in Cort following burn wound sepsis prolongs the survival of translocated bacteria in the MLN of rats (23, 27). The role of other hormones in pathogenesis of infectious diseases and, in particular, enteric infections was described recently (34). These reports suggest that products of HPA can directly influence growth and virulence of bacteria. In a recent study, catecholamines were shown to promote growth of Escherichia coli (34). However, whether glucocorticoids directly affect bacterial growth or virulence in EtOH and burn injury remains unknown. It is also likely that elevated Cort levels following a combined insult of EtOH and burn injury may impair normal intestinal peristalsis by promoting stasis. Impaired peristalsis is associated with increased bacterial growth and their translocation in both human beings and animals.

The fact that T cell-mediated immunity is critical to defense against bacterial infection, including the bacteria derived from intestine, is supported by many previous studies (8, 14, 31, 38, 45). Sibley and Jerrells (46) have shown that the loss of lymphoid cells after chronic EtOH abuse diminishes host resistance to enteric pathogens. Others have suggested that adoptive transfer of T cells provides protection against a number of bacterial infections (43). In addition, previous studies have shown an increase in spontaneous bacterial translocation from intestine to extraintestinal organs in athymic homozygous (nu/nu) nude mice compared with heterozygous strains (nu+/+) (41). Furthermore, recent findings from our laboratory have shown that depletion of T cells in healthy rats resulted in increased bacterial accumulation in MLN (6). A similar T cell depletion in EtOH- and burn-injured rats further enhanced bacterial accumulation in MLN and in other distant organs, including spleen and blood (6). Bacterial translocation is an ongoing process, and in healthy conditions, a few bacteria are known to translocate to MLN. However, these bacteria do not survive because of intact immune defense, and, thus, MLN from healthy animals remains relatively sterile. Because T cell-mediated immunity is critical to defense against enteric bacteria, impaired MLN T cell function as observed after EtOH and burn injury would be expected to contribute to a decrease in bacterial clearance and an increase in bacterial multiplication, resulting in their accumulation.

In summary, our present results suggest that EtOH intoxication prior to burn injury augments Cort release, which in turn suppresses T cell function by inhibiting p38 and ERK pathway. This leads to increased bacterial accumulation in MLN. MLN is the central lymph node that connects various parts of the intestine and therefore plays a critical role in clearing bacteria originating from the intestine. Thus any alterations in MLN T cell function may impair the local immune defense, resulting in bacterial multiplication and accumulation in MLN.

GRANTS

This study was supported by National Institute on Alcohol Abuse and Alcoholism Grants AA-12901 (to M. A. Choudhry) and AA-12034 (to E. J. Kovacs).

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AJP-Regul Integr Comp Physiol • VOL 289 • JULY 2005 • www.ajpregu.org


