Role of Corticosterone in the Enhancement of the Antibody Response after Acute Cocaine Administration

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ABSTRACT
A model has been developed in which acute cocaine administration results in an enhanced T-dependent antibody response to sheep erythrocytes. This enhancement occurs when cocaine (30 mg/kg, twice in 1 day) is administered 1 or 2 days before sensitization with antigen, in mice older than 16 wk. Acute cocaine has been shown to elicit a rise in serum corticosterone, and the administration of exogenous corticosterone, under similar conditions as cocaine, also results in a similar immunoenhancement. Further evidence in support of a role by corticosterone is the lack of an enhancement in adrenalectomized mice and the ability of α-helical corticotropin releasing factor to block the enhancement by cocaine. The role of concomitant epinephrine release from the adrenal was addressed by adrenal demedullation. Eliminating epinephrine, but not corticosterone release, had no effect on the cocaine-induced immunoenhancement. The evidence presented provides support for a major role by corticosterone in mediating cocaine’s effects on at least one measure of immune function, the T-dependent antibody response.

Cocaine is one of the most widely abused drugs in our society, exerting strong behavioral effects through the blockade of monoaminergic reuptake in the brain. Coincidental with an increase in drug abuse is the continuing spread of HIV infection. There appears to be an association between drug abuse populations and the development of AIDS, thus leading to the belief that the use of such drugs may serve as a cofactor (Donahoe and Falek, 1988; Donahoe, 1990). The question remains whether it is the lifestyle of the drug user (needles, nutrition, sexual practices, etc.), the effects of drugs of abuse on the immune system or a combination of factors that may lead to increased susceptibility to HIV and the progression to AIDS. However, it has not been adequately shown that drugs of abuse affect immune function to a degree that might predispose one to actual changes in HIV infectivity. As discussed below, the literature on cocaine and immune function presents a confusing range of contradictory effects on a variety of immune function measures. The difficulties in interpretation and comparison are due to the different exposure regimens (including dose, route, time-course, etc.), different animal models (including sex, strain, and species), and different immune parameters (including antigen-dependent primary responses, mitogen-stimulated lymphoproliferation and host-resistance models).

There are in vitro studies aimed at addressing the direct effects of cocaine on immune function. Many of these studies tend to investigate changes in lymphocyte proliferative responses to mitogen stimulation (Klein et al., 1988; Delaflente and DeVane, 1991). However, significant changes in vitro only occur at doses beyond the range obtainable in vivo. This is also demonstrated in the in vitro antibody response (Holsapple et al., 1993). Therefore, the relevance of these effects to in vivo exposure is questionable as are the direct effects of cocaine on immune function. These results have prompted some investigators to propose that cocaine’s effects on immune function are due to indirect mechanisms (Watzl and Watson, 1990).

Cocaine is shown to produce immunotoxicity in vivo under a variety of experimental conditions. Suppression has been demonstrated in lymphocyte proliferation (Pillai et al., 1991; Bayer et al., 1995), macrophage function/phagocytosis (Ou et al., 1989; Pillai et al., 1991; Shen et al., 1994) and natural

ABBREVIATIONS: HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; SRBC, sheep red blood cells; CRF, corticotropin-releasing factor; α-h-CRF, α-helical corticotropin-releasing factor[9–41]; EBSS, Earle's balanced salt solution; AFC, antibody forming cells; SPLC, splenocytes; HPA, hypothalamic-pituitary-adrenal; ADX, adrenalectomy; AMX, adrenal demedullation; ACTH, corticotropin; VH, vehicle.
killer cell activity (DiFrancesco et al., 1990). Humoral immunity as measured by antibody production is generally suppressed (Watson et al., 1983; Ou et al., 1989; DiFrancesco et al., 1992; Shen et al., 1994). Cell-mediated responses such as cytotoxic T lymphocyte activity and delayed-type hypersensitivity result in suppression (Watson et al., 1983; DiFrancesco et al., 1990) as well as no effect (Holsapple and Munson, 1985; Starec et al., 1991). Actual host resistance changes include slight decreases in viral resistance (DiFrancesco et al., 1990; Starec et al., 1991), a slight increase in tumor growth (Ou et al., 1989) and no effect on Streptococcus pneumonia infectivity or tumor growth (Havas et al., 1987). Recently, the ability of cocaine to alter cytokine production has been investigated (DiFrancesco et al., 1992; Wang et al., 1994); however, the immunological implications of this complex profile of activity are still unclear.

Although cocaine definitely appears to have effects on immunocompetence, there is a lack of consistency in these effects. A review of cocaine's effects on immune function also demonstrates such a disparity on multiple immune parameters (Watzl and Watson, 1990). Our laboratory alone, with a single measure, the T-dependent antibody response to SRBC, has shown an enhancement, no effect, and a suppression under various conditions. We have speculated that this differential profile of activity is a reflection of a number of different mechanisms. The suppression has been shown to be a result of the production of reactive metabolites and liver toxicity via a minor metabolic pathway (Jeong et al., 1995; 1996) and indirect immune suppression through serum born transforming growth factor-β (Matulka et al., manuscript in preparation). This occurs only under high dose, chronic exposure or by increasing the role of the minor metabolic pathway using esterase inhibitors or cytochrome P-450 inducers. In general, initial studies showed no effect on immune function under normal conditions (Holsapple et al., 1993), which may be due to suboptimal conditions of exposure or the possibility that different mechanisms are acting simultaneously and thereby confounding results with multiple indirect mediators. Current work is focused on the enhancement of the T-dependent antibody response. Our first objective was to develop an acute model, which consistently and reproducibly demonstrated an enhancement with cocaine, to best elucidate a mechanism of action. As emphasized in the “Discussion,” this immunoenhancement can have profound adverse consequences and should be considered an important component of cocaine-induced immunotoxicity. This acute regimen may also more adequately reflect a more typical pattern of cocaine use (binge or occasional use, not chronic). Once a model was established, we were led to hypothesize that the mechanism of immunoenhancement would likely involve another indirect mechanism, centered around cocaine's potential to produce changes in neuroendocrine status.

Materials and methods

Animals. All studies used virus-free female B6C3F1 mice purchased from either the National Cancer Institute (Frederick, MD) or Charles River Laboratories (Wilmington, MA). Upon arrival, mice were randomized into plastic cages with filter bonnets and sawdust bedding, followed by a 1-week quarantine period. Mice were housed either four or five per cage with food (Purina Lab Chow, St. Louis, MO) and water ad libitum. Animal holding rooms were maintained at 21 to 24°C and 40 to 60% relative humidity with a 12-hr light/dark cycle. All experiments used mice at either 8 to 10 wk of age or 16 to 20 wk of age, as specified.

ADX and AMX mice were purchased from Charles River Laboratories along with normal and sham animals from the same lot. They were maintained as above with the exception that adrenalectomized mice received 0.9% saline as drinking water.

Chemicals. Cocaine hydrochloride was obtained through the National Institute on Drug Abuse (Research Triangle Park, NC) and prepared in saline. Corticosterone was purchased from Sigma Chemical Co. (St. Louis, MO) and prepared as a suspension in saline containing 0.2% methylcellulose and 0.2% Tween 80. The CRF antagonist (oh-CRF [9–41]) was also purchased from Sigma. SRBC were purchased from Colorado Serum Co. (Denver, CO) and prepared in EBSS.

Administration of chemicals. All acute exposures occurred on a particular day before sensitization, as specified. Cocaine exposure involved the i.p. injection of 30 mg/kg administered twice that particular day (9 A.M. and 3 P.M.). Corticosterone was administered by oral gavage at either 50 or 100 mg/kg given once that day (12 noon). All treatments were prepared fresh and at a concentration that mice received 0.01 ml/gram body weight. The oh-CRF was given as 10 μg/5 μl hCRF20 per mouse, via intrathecal injection, 5 min before cocaine administration.

In vivo antibody response. On day 0, mice were sensitized with antigen at 12 noon and the day of chemical exposure is expressed relative to this time point. The standard T-dependent antigen concentration was 5 × 10⁶ SRBC in 0.5 ml of EBSS administered via i.p. injection. The antibody response was determined on day 4 after sensitization. Single cell suspensions were prepared from each spleen in 3 ml of EBSS, then washed and resuspended in 3 ml of EBSS, and the cell number was counted on a Coulter counter. Spleen cells were diluted 30-fold by resuspending a 100-μl aliquot of each suspension in 2.9 ml of EBSS. The number of AFC was determined using a modified Jerne plaque assay, as described in detail by Holsapple (1995). Briefly, 0.05% DEAE-dextran (Pharmacia, Piscataway, NJ) was added to 0.5% agar (DIFCO, Detroit, MI) in EBSS and was maintained at 47°C in individual 12 × 75-mm heated tubes containing 400 μl of the agar solution. Additionally, each tube received 50 μl of a diluted cell suspension, 25 μl of indicator SRBC and 25 μl of guinea pig complement. Each tube was immediately vortexed, poured into a 100 × 15-mm petri dish, and the solution was covered with a 45 × 50-mm coverslip. After solidifying, the petri dishes were incubated at 37°C for 3 hr. After incubation, the AFCs, as hemolytic plaques, were enumerated at 6.5× magnification using a Belloco plaque viewer and expressed as IgM AFC/10⁶ SPLC.

Serum corticosterone. The concentration of serum corticosterone was determined by a radioimmunoassay kit (Diagnostic Products Corp., Los Angeles, CA). Serum samples were obtained from individual mice at a given time after chemical treatment. Within a two minute period mice were individually brought into the necropsy room, anesthetized with CO₂ and bled by cardiac puncture. All experiments were done with a staggered pattern of dosing so all collection occurred between 11 A.M. and 1 P.M. Serum samples were stored at −20°C until assayed.

Statistics. The data are presented as the mean ± S.E. for each treatment group. Each study is representative of at least two trials. Data were evaluated using a parametric analysis of variance. When significant differences occurred, treatment groups were compared to the vehicle control using a Dunnett’s two-tailed t test. A Duncan’s multiple range analysis was used when multiple controls were present. Significant differences are marked where a *P < .05 and **P < .01 compared to respective controls.

Results

Time- and dose-dependent enhancement of the T-dependent antibody response after acute cocaine exposure. A model was developed in which the acute admin-
istration of cocaine, twice in 1 day (6 hr apart), consistently resulted in an enhanced T-dependent antibody response to SRBC. The enhancement occurs when cocaine is given before sensitization with antigen, in mice at least 16 wk of age. This effect, represented throughout our report, results in an enhancement ranging from 25% to more than 100%.

Time of cocaine administration relative to sensitization is specific to 1 or 2 days before antigen. These time points (day -1 and -2) represent the day of the two doses of cocaine generally given at 9 A.M. and 3 P.M. with a 12 noon sensitization occurring on day 0. The time-dependence of the immunoenhancement is demonstrated in figure 1. Both time points appear to be equally effective in achieving a maximal response in a given assay. Initially, either time point was used and both are represented in various trials. Later, the day -1 time point was chosen for the model simply out of convenience. The dose-dependence of cocaine administration is specific to 30 mg/kg, as shown in figure 2. Only this dose appears effective in eliciting a statistically significant enhanced antibody response. As previously stated this dose is given twice, a regimen that also appears to be necessary (data not shown).

**Age specificity of mice in the cocaine-induced immunoenhancement.** The enhancement of the T-dependent antibody response in the model described in the previous section is also specific to the age of the mice. The model uses mice generally between the ages of 16 to 20 wk, and has been demonstrated in mice as old as 36 wk. However, the enhancement does not occur in mice of the commonly used 8 to 10 wk of age. As such, it is important to emphasize that it is the absence of the enhancement in young mice that is the age-restricted event. Figure 3 is an example of the inability of mice in this age group to yield an enhanced antibody response under identical conditions of the model for 16- to 20-wk-old mice. The lack of an immunoenhancement in 8- to 10-wk-old mice is not due to a shift in time- or dose-dependent responsiveness (data not shown).

**Cocaine-induced increases in serum corticosterone.** The 30-mg/kg dose of cocaine used to evaluate a change in antibody production does elicit a rise in serum corticosterone. As shown in figure 4, this rise is significant compared to vehicle responses, which are also higher than naive mice. There is obviously some stress involved in the handling and dosing procedure. However, cocaine is responsible for an additional rise presumably through its direct activation of the HPA axis above that of the handling stress. A second injection of cocaine 6 hr after the first is able to produce the same rise in serum corticosterone (data not shown). Also, a similar rise in serum corticosterone occurs in both 8- to 10-wk-old mice and 16- to 20-wk-old mice after cocaine (data not shown).

**Exogenous corticosterone mimics the effects of cocaine in the T-dependent antibody response.** Because serum corticosterone is increased after acute cocaine, the direct effect of corticosterone itself was examined. When exogenous corticosterone is administered under similar conditions as cocaine, a similar enhancement of the T-dependent antibody response occurs. Specifically, corticosterone was given only once at the time point between the two doses of cocaine. As shown in figure 5, corticosterone produces a biphasic dose-response curve, as does cocaine. The doses of 50 and 100 mg/kg produce a significant enhanced antibody re-

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**Fig. 1.** Time-dependent effects of acute cocaine administration, relative to sensitization, on the T-dependent antibody response. Cocaine (30 mg/kg) or vehicle (saline) was administered twice (6 hr apart) on a particular day relative to the day of sensitization (day 0) via i.p. injection. On day 4, the number of AFC was determined as described in “Materials and methods.” Each group represents the mean ± S.E. of four animals, age = 19 wk. **Significantly different from respective vehicle control, P < .01.

**Fig. 2.** Dose-dependent effects of acute cocaine administration on the T-dependent antibody response. Cocaine was administered at doses of 10, 20, 30, 40, 50 and 60 mg/kg, twice in 1 day (6 hr apart), via i.p. injection. Treatment occurred 1 day before sensitization (day 0) and the number of AFC was determined on day 4, as described in “Materials and methods.” Each group represents the mean ± S.E. of four animals, age = 18 wk. **Significantly different from vehicle (VH) control, P < .01.
response, although a dose of 200 mg/kg is actually suppressive. Interestingly, both 50 and 100 mg/kg have proven equally effective. Administration of corticosterone also follows the same time course as cocaine in producing an immunoenhancement (data not shown). The age-related effect is also apparent, where the enhancement does not occur in the 8- to 10-wk-old mice after exogenous corticosterone (data not shown).

**Blockade of the cocaine-induced immunoenhancement with adrenalectomy.** Although there is a good correlation between corticosterone and the enhancement of the antibody response observed in cocaine-treated mice, it was necessary to demonstrate a more causal relationship. ADX

**Fig. 3.** Age-related specificity in the model of cocaine-induced immunoenhancement. Mice of two age groups, (A) 8 wk old and (B) 17 wk old, were compared in their T-dependent antibody responses after acute cocaine. Cocaine (30 mg/kg) or vehicle (saline) was administered twice in 1 day (6 hr apart) via i.p. injection, 2 days before sensitization (day 0). On day 4, the number of AFC was determined as described in "Materials and methods." Each group represents the mean ± S.E. of four animals. *Significantly different from vehicle control, P < .05.

**Fig. 4.** Cocaine-induced increase in serum corticosterone. Cocaine (30 mg/kg) or vehicle (saline) was administered to mice, followed by serum collection at specific time points. Serum collection and analysis was performed as described in "Materials and methods" and expressed as serum corticosterone concentration (ng/ml). Each time point represents the mean ± S.E. of a separate group of four mice. Each cocaine time point was compared to the corresponding vehicle for significance where *P < .05 and **P < .01.

**Fig. 5.** Administration of exogenous corticosterone mimics the effects of cocaine in the T-dependent antibody response. Cocaine (15 and 30 mg/kg) or vehicle (saline) was administered twice in 1 day (6 hr apart) via i.p. injection. Corticosterone (25, 50, 100 and 200 mg/kg) or vehicle (saline, 0.2% methylcellulose, 0.2% Tween 80) was administered once (midpoint of cocaine injections) via oral gavage. All doses were given 1 day before sensitization (day 0) and the number of AFC was determined on day 4, as described in "Materials and methods." Each group represents the mean ± S.E. of four animals, age = 16 wk. Both cocaine and corticosterone were compared to their corresponding vehicles for significance where *P < .05 and **P < .01.
proven to be the most effective means of addressing the relative involvement of corticosterone, as the adrenal gland is both the end of the HPA axis and the source of corticosterone. Adrenalectomy itself had no effect on the antibody response, as evidenced by the consistency of the vehicle treatments. Cocaine was administered to normal, sham and adrenalectomized mice as in the established model (fig. 6). As expected, acute cocaine resulted in an enhanced antibody response in the normal and sham animals. However, in the adrenalectomized group the enhancement was completely prevented. This provides strong support for the role of corticosterone in the cocaine induced enhancement of the T-dependent antibody response.

Adrenal demedullation does not attenuate the cocaine-induced immunoenhancement. Epinephrine is also released from the adrenal, along with corticosterone, and both are affected by adrenalectomy. AMX eliminates the source of epinephrine, but not corticosterone. With corticosterone still present, the antibody response is enhanced in normal, sham and demedullated animals after cocaine (fig. 7). This observation further suggests that it is corticosterone, and not epinephrine, from the adrenal that is required for the enhancement to occur.

Central blockade of HPA axis activation also supports a role by corticosterone. The central administration of αh-CRF, 5 min before cocaine administration, antagonizes further activation of the HPA axis after increased CRF. The vehicle responses and αh-CRF alone did not alter the antibody response in this paradigm (fig. 8, inset). The cocaine-induced enhancement in this study was completely blocked by pretreatment with αh-CRF (fig. 8). This is consistent with a role for increased corticosterone, after HPA axis activation by cocaine, in the enhanced T-dependent antibody response.

Discussion

Initial studies revealed cocaine’s ability to enhance the T-dependent antibody response to SRBC after acute exposure. A model was developed as a result of assessing the parameters necessary to observe this effect. The immunoenhancement was shown to be both time- and dose-dependent, as well as age specific. As presented in our model, acute cocaine enhances the T-dependent antibody response to SRBC under the following conditions: 1) a dose of 30 mg/kg cocaine is administered twice in 1 day; 2) the time of administration must occur 1 or 2 days before sensitization with antigen (day 0) and 3) the age of the mice used are approximately 16 wk old or more, as opposed to 8- to 10-wk-old mice, which are more commonly used in immunotoxicological studies.

As previously stated, cocaine itself has been shown to exert a wide variety of effects on multiple immune parameters. In general, immunomodulation by cocaine and other xenobiotics is associated with a suppression of immune function, particularly the T-dependent antibody response. In our model we see a consistent enhancement within the range of 25 to 100%. An enhancement of an immune response, although sounding beneficial, may in fact be equally detrimental if it is associated with allergy, hypersensitivity, and autoimmune disease, or if it occurs at the expense of other immune functions. For example, in HIV infection, an increase in antibody response...
in the acute model. A more plausible mechanism for the current model would be the indirect effects on immune function via changes in neuroendocrine status. Although still in its infancy, there is a large body of literature demonstrating that different stressors alter the levels of various neuroendocrine factors that in turn interact with the immune system to disrupt function. A few general reviews on the subject include Fuchs and Sanders (1994), Ader et al. (1990) and Dunn (1989). How all these neuroendocrine factors affect immune function is not always consistent and interpretations are often difficult due to the complexity of the interactions occurring. The influences of neuroendocrine modulation on immune function, as measured by the antibody response, have been demonstrated for other drugs of abuse such as morphine (Pruett et al., 1992) and ethanol (Han and Pruett, 1996). However, it appears the two major pathways that exist for neuro-endocrine-immune interactions are HPA axis activation and sympathetic nervous system outflow. The body's stress response shares these two final common pathways resulting primarily in an increase in plasma corticosterone and a release of catecholamines, as well as at least 17 other neuropeptides with immunomodulatory potential (Khansari et al., 1990). The administration of cocaine mimics the stress response as measured by neuroendocrine changes (DiPaolo et al., 1989). Although the exact mechanism is unknown, cocaine's central nervous system stimulation activates the HPA axis in the hypothalamus and via CRF stimulates corticotropin (ACTH) secretion from the pituitary, which acts on the adrenal cortex to release corticosterone (Rivier and Vale, 1987; Sarnyai et al., 1992).

Therefore, in our model, cocaine acts as a stressor resulting in activation of the HPA axis. The dose used in the acute model, 30 mg/kg, produces obvious behavioral activation including increased locomotor activity and startle response. The end result of HPA axis stimulation is an increase in serum corticosterone, which is shown in figure 4. There is no attenuation in the rise in serum corticosterone after the second dose of cocaine, 6 hr later, as supported by Torres and Rivier (1992). Our investigation into the mediators of cocaine's enhancement of the T-dependent antibody response began with the HPA axis, and specifically with corticosterone, as it is commonly implicated in altering immune function (Pruett et al., 1993). As previously stated, cocaine influences the levels of numerous potential factors, any or all of which could also play a role. We chose to administer exogenous corticosterone to see if it could mimic the effects of cocaine. Although corticosterone is often implicated as an indirect mediator of immunological change, we were unable to find where the administration of exogenous corticosterone in vivo was shown to alter immune function. As shown in the figure 5, administration of corticosterone caused an enhancement in the antibody response that paralleled the profile of activity with cocaine, in that it was both dose- and time-dependent. This provided a good correlation between corticosterone elevation and the immunoenhancement.

It is interesting to note the age-related differences in the enhancement. Recall that the model for cocaine required older mice (>16 wk) as opposed to younger mice (8–10 wk). However, serum corticosterone increased similarly for both age sets, but exogenous corticosterone only enhanced the antibody response of the older mice, analogous to cocaine. This suggests that cocaine's central activation of the HPA axis is the same, but a different level of immune sensitivity to glucocorticoids exists. It may be due to differential corticosterone sensitivity in the two age groups, or changes in other factors that either alter corticosterone responsiveness or mask corticosterone's effects through conflicting effects on immune function. One possible explanation might involve the other major pathway for interaction: sympathetic innervation of the spleen and neurotransmitter activity on immune cells. At this time, we can only speculate because this is not the area of current focus.

Although a nice correlation between corticosterone and
immoenahancement exists, further information was needed to implicate a causal relationship. Studies focused on blocking the corticosterone effect, and adrenalectomy proved to be the most effective. Adrenalectomy completely blocked cocaine’s ability to enhance the T-dependent antibody response, providing strong support for corticosterone’s role (fig. 6). Note that adrenalectomy itself had no effect on immune function. Further, the potential involvement of ACTH directly is not supported by the adrenalectomy or exogenous corticosterone data, as levels of ACTH would be at either high (ADX) or low (bolus corticosterone) extremes, yet the enhancement remains consistent with corticosterone’s presence. We are aware that epinephrine is also released from the adrenal, specifically from the adrenal medulla. The possible concomitant involvement of sympathetic modulation from this source was addressed by adrenal demedullation (fig. 7). The elimination of epinephrine, but not corticosterone, had no effect on the cocaine-induced enhancement. Thus corticosterone appears to be a, if not the, major factor in this no effect on the cocaine-induced enhancement. The elimination of epinephrine, but not corticosterone, had no effect on the cocaine-induced enhancement. Thus corticosterone appears to be a, if not the, major factor in this phenomenon. Further evidence for this conclusion stems from studies using ah-CRF, a central CRF receptor antagonist that blocks further activation of the HPA axis (Rivier et al., 1984). As shown in figure 8, blockade of central HPA axis activation does prevent the enhancement by cocaine, as expected. RU-486 is a glucocorticoid receptor antagonist, which directly prevents corticosterone activation of its receptor. In preliminary studies, RU-486 was also able to block the cocaine-induced immunoenhancement (data not shown).

The apparent involvement of corticosterone in an enhanced antibody response may seem odd, because corticosterone is generally associated with a suppression of immune parameters. For that matter, most stressors that elevate corticosterone to similar levels or less are suppressive (Pruett et al., 1993; Khansari et al., 1990), including other drugs of abuse such as morphine (Pruett et al., 1992) and ethanol (Han and Pruett, 1996). Adding to the complexity is that our corticosterone levels of 800 to 1000 ng/ml are on the high end, although still resulting in an enhancement. The vehicle-induced levels are also elevated above what many stressors cause yet no changes in antibody production occur in relation to naive animals. Another seemingly inconsistent observation is the broad plateau for producing the enhancement in the exogenous corticosterone dose response curve. In reviewing the literature on corticosterone levels and immunomodulation, Pruett et al. (1993) concluded that serum levels of corticosterone are not necessarily predictive of immunological outcome. Therefore, we believe it may not be the absolute level of corticosterone that is of the greatest importance, rather, it seems there is a window for corticosterone sensitivity that is critical. This window may be specific to the timing of immunological events and may require a particular duration of exposure to a minimal level or percent increase. Our acute regimen produces two (<1 hr) spikes of corticosterone after cocaine administration; however, exogenous corticosterone is only given once and over a larger dose range. A bolus dose of corticosterone will result in higher blood concentrations for a longer duration. However, the total time that corticosterone levels persist within a particular range may be similar to the two regimens (i.e., “area under the curve” of exposure may be important).

It is difficult to speculate as to how much corticosterone the splenocytes themselves are actually in contact with as a result of such circulating levels. This is due to the observations that the spleen is somehow protected from bolus doses of corticosterone, and the vast majority of corticosterone in the circulation is bound to proteins, either high-affinity, low-capacity corticosterone binding globulin or low-affinity, high-capacity albumin (Dunn, 1989). These proteins serve to expand the range of concentrations to which tissues could be exposed after rapid increases, and the result is also a decrease in the net concentrations to which lymphocytes may be exposed. Other physiological factors that may play a role in actual exposure conditions are receptor density changes and the complimentary or permissive actions of other mediators that facilitate corticosterone’s effects, or those that may antagonize corticosterone’s effects. The complexity of corticosterone exposure in vivo is poorly understood, and is only now beginning to be addressed. Thus, it is possible for our model that only so much corticosterone exposure in the spleen occurs at one time, but it is the pattern/duration of exposure that is important. This speculation makes sense in an overall scheme; for example, if splenocytes were not somewhat protected, then any daily stressor would simply increase corticosterone, flood the system and have a profound impact on immune function. This is clearly not the case normally; however, it may be analogous to what happens during debilitating chronic stress where immune function is impaired. The suppressive dose of 200 mg/kg may overwhelm the physiological capacity for corticosterone regulation and act more as a therapeutic dose, causing suppression. Therefore, a window of opportunity exists, possibly aided by the actions of other factors, for the exposure conditions in our model to permit adequate levels and duration of exposure to corticosterone for splenocytes to be affected.

To summarize, the results of our investigation indicate that cocaine can consistently and reproducibly cause an enhancement of the T-dependent antibody response, and that this effect is mediated by the release of corticosterone. The next step in characterizing this neuroendocrine mechanism of immunomodulation will be to determine the cellular target that is primarily responsible for this effect. As reviewed by Holsapple (1995), the T-dependent antibody response is critically dependent on the cooperativity of B cells, T cells (principally T helper cells) and macrophages. In general, chemicals that suppress the T-dependent antibody response have been characterized to selectively target a specific type of immunocompetent cell (Holsapple 1995). Identifying the primary cellular target responsible for the cocaine-induced enhancement will allow for more focused studies to characterize the mechanism of action.

References


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