charge. Atropine blocked the depolarization (Fig. 2B). These findings indicate that this potential is a slow muscarinic excitatory postsynaptic potential (EPSP).

In addition to generating a slow EPSP, the stimulus also reduced the AHP after activation of the cell by depolarizing current pulses, indicating a reduction in calcium-activated potassium conductance. In Fig. 2C an AHP was elicited before and 4 seconds after pathway stimulation (S) that caused a small decrease in the amplitude of the AHP. In the presence of eserine (trace 2 in Fig. 2C) the same stimulus caused a much larger reduction (arrow). Atropine entirely blocked the stimulus-induced depression of the AHP (trace 3 in Fig. 2C). Pathway stimulation also attenuated accommodation of spike discharge during long direct depolarizing current pulses, and this effect was markedly enhanced by eserine and blocked by atropine (Fig. 2D). Both the AHP and the accommodation provided very sensitive measures of cholinergic activity, since dramatic effects on these parameters could be seen in the absence of any change in membrane potential (*16*).

These results demonstrate that electrical stimulation of sites known to contain cholinergic fibers can evoke synaptic responses in hippocampal pyramidal cells that exactly mimic all the postsynaptic effects of exogenously applied acetylcholine. Thus the findings fulfill an important criterion in establishing ACh as a neurotransmitter and indicate that the pharmacological effects produced by ACh are indeed of physiological relevance. Except for two reports (*8, 17*), chemical synapses in the mammalian brain have been found to increase membrane conductance. The cholinergic slow EPSP reported here is nonclassical in that at least two types of potassium conductances (calcium-activated and M-current) are blocked; both exert powerful braking actions over repetitive cell discharge (*2, 14, 15*). As a consequence, during cholinergic synaptic activity, pyramidal cells fire many more action potentials to depolarizing stimuli, even though the synaptic action may cause little or no depolarization of the cell. Norepinephrine (*15*) and serotonin (*18*) have also been found to facilitate repetitive discharge.

Early iontophoretic studies indicated that ACh could decrease resting potassium conductance in neocortical neurons (*3*), and a number of recent studies, primarily of invertebrate neurons and neurons from the vertebrate peripheral nervous system, have emphasized the importance of voltage- and calcium-dependent potassium conductances as targets for neurotransmitter action (*19*). The present results indicate that such nonclassical actions also occur in neurons of the mammalian brain following the synaptic release of ACh.

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## Stress-Induced Suppression of Immunity in Adrenalectomized Rats

Abstract. *Stress-induced suppression of lymphocyte stimulation by phytohemagglutinin was demonstrated in isolated lymphocytes and in cultures of whole blood from adrenalectomized rats. The results demonstrate that corticosteroid independent mechanisms participate in the suppression of lymphocyte function by stressors. Stress-induced lymphopenia, however, was found to be adrenal dependent, indicating that the modulation of immunity by stress is complex and multidetermined.*

We showed previously that a graded series of stressors suppressed lymphocyte function in rats (*1*). Secretion of corticosteroids has long been considered to be the mechanism of stress-induced modulation of immunity and related disease processes (*2–4*). Concurrent increased adrenal activity, suppressed measures of immunity, and increased illness susceptibility have been reported (*5–7*). These studies have suggested that lymphocyte function is suppressed by stress-induced adrenal activity. In the present study we investigated the effects of stressors in adrenalectomized rats to determine if the adrenal is required for stress-induced suppression of lymphocyte function.

We used a total of 160 W/Fu rats (Microbiological Associates) and a four-times-four experimental design (ten rats per group). The four groups of rats studied consisted of nonoperated, andrenalectomized, sham adrenalectomized, and adrenalectomized animals with a corticosterone pellet. The four treatments—home-cage control, apparatus control, and low-shock and high-shock animals—

were identical to those used in our previous study (*1, 8*). Adrenalectomy and sham adrenalectomy were performed by standard techniques (*9*). Rats in the adrenalectomized group with a pellet of corticosteroid were adrenalectomized as described, and a pellet consisting of 50 mg of corticosterone combined with 50 mg of cholesterol (*10*) was implanted subcutaneously at the completion of surgery. This last group was included to test for stress effects on lymphocyte stimulation in animals with fixed levels of corticosteroids (*11*). Two weeks were allowed for recovery from the operative procedures. All animals were given free access to food, tapwater, and saline. All experiments were conducted at the same time of day to control for possible circadian effects (*12*). After the shock period, the rats were randomly removed from the apparatus or home cages and anesthetized with ether and exsanguinated within 3 minutes with the use of preservative-free heparin. Portions of blood from each animal were used for each of the studies in vitro. Absence of adrenal tissue was confirmed by necropsy and corticosteroid levels.

Total white blood cell and differential counts were performed by standard techniques. Micromethods developed by Keller and co-workers were used to assess PHA (purified phytohemagglutinin; Wellcome Reagents) induced stimulation of lymphocytes isolated from rat periph-

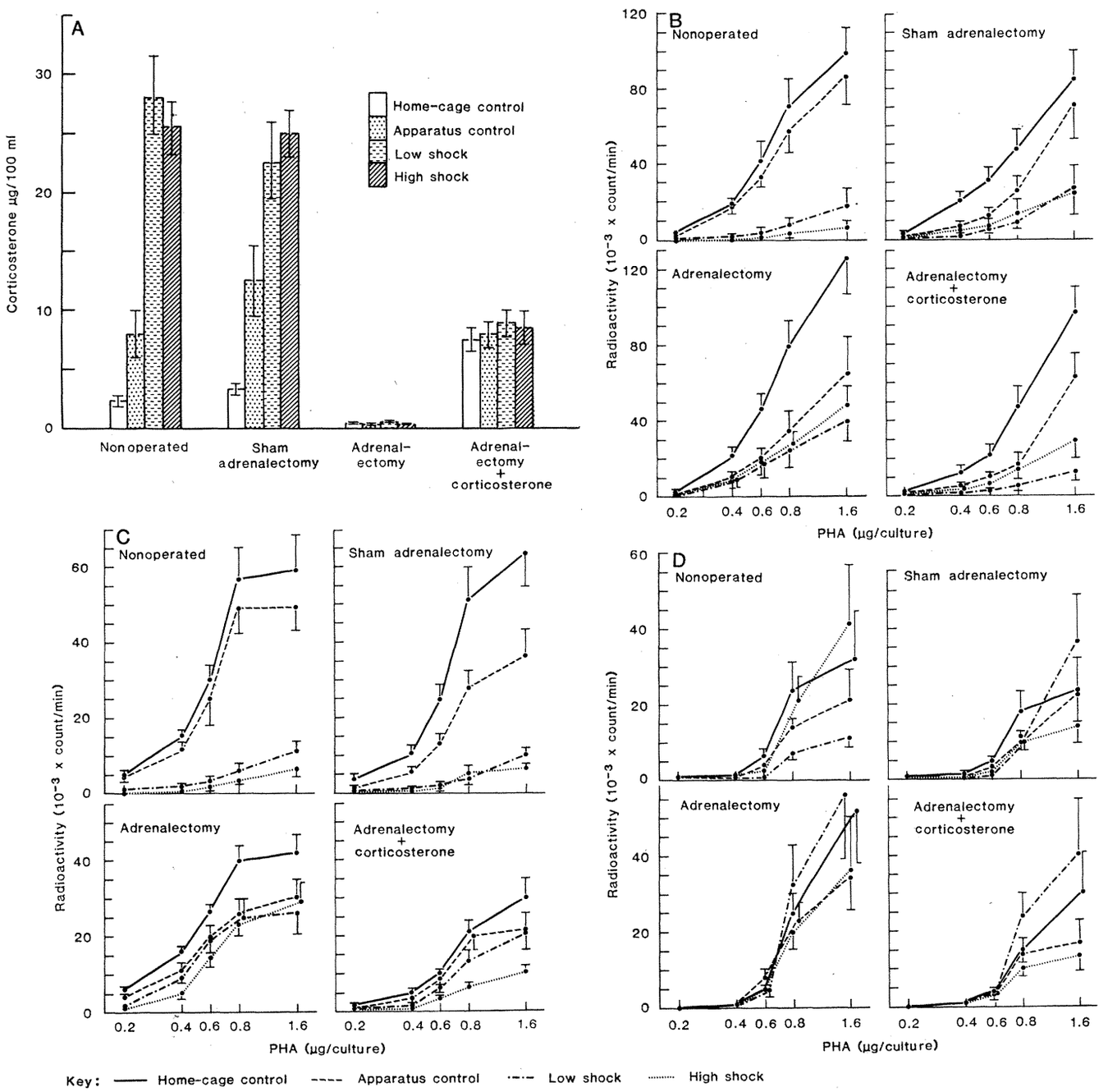


Fig. 1. (A) Effects of stressors on corticosterone concentrations in nonoperated, sham adrenalectomized, adrenalectomized, and adrenalectomized with pellet groups (mean ± standard error). (B) Stimulation of isolated peripheral blood lymphocytes by PHA for each of the four operative groups and four treatment procedures. Data (means ± standard errors) are represented as Δcpm. (C) Stimulation of lymphocytes in whole blood by PHA for each of the four operative groups and four treatment procedures. Data (means ± standard errors) are represented as Δcpm. (D) Stimulation of splenic lymphocytes by PHA for each of the four operative groups and four treatment procedures. Data (means ± standard errors) are represented as Δcpm.

eral blood (*13*) and stimulation of lymphocytes in whole blood cultures (*14*). Stimulation of splenic lymphocytes was carried out according to the method of Sell *et al.* (*15*) and Hem (*16*). All cultures were prepared in triplicate. A full dose response to PHA was used with five concentrations of mitogen in each lymphocyte stimulation assay. For the isolated peripheral blood and spleen cell assays we used $5 \times 10^5$ lymphocytes per culture. The lymphocyte stimulation data in Fig. 1 and the data used for the statistical analysis were expressed as counts per minute in the stimulated cultures minus counts per minute in the corresponding unstimulated cultures. Plasma corticosterone concentrations were measured by radioimmunoassay (RSL, Carson, California).

There was a progressive increase in corticosterone with increasing stress in both of the groups with adrenals (Fig. 1A); no corticosterone was detected in the adrenalectomized group, and the concentration of corticosterone in the adrenalectomized group that received the corticosterone pellets was constant. The concentration of corticosterone in the sham adrenalectomy group indicated that the 2-week postoperative period was sufficient to allow recovery to baseline corticosteroid levels and that the operative procedure did not affect stress-related corticosterone responses. The absence of corticosterone in the adrenalectomized group confirmed total adrenalectomy. The adrenalectomized rats that received the corticosterone pellets showed intermediate corticosterone levels which were nonresponsive to the stress conditions.

In both the nonoperated and sham adrenalectomy groups, there was a progressive stress-induced lymphopenia (Table 1) ($F = 2.53$, d.f. = 3,67; $P < 0.06$). There were no stress-related changes in lymphocyte number in the adrenalectomized group or the group that was adrenalectomized and given pellets ($F = 0.31$, d.f. = 3,67; not significant). Lymphopenia following exposure to stress was described as early as 1937 (*17*) and has been associated with adrenal hypertrophy and involution of the thymus and spleen (*5*). Stress-induced leukopenia can be prevented by adrenalectomy in mice (*18*). The present study demonstrates that stress-induced lymphopenia in the rat occurs in association with stress-induced secretion of corticosteroids and can be prevented by adrenalectomy (*19*).

The stressful conditions suppressed the stimulation of isolated lymphocytes by PHA in the adrenalectomized animals (Fig. 1B). The stressors similarly suppressed PHA-induced lymphocyte stimulation in nonoperated animals, replicating the data in our earlier report (*1*). Suppression of lymphocyte stimulation also occurred in the sham adrenalectomy group and in adrenalectomized animals with steroid replacement. Analysis of variance (ANOVA) revealed a highly significant treatment effect ($F = 34.59$, d.f. = 3,135; $P < 0.0001$) and group effect ($F = 4.66$, d.f. = 3,135; $P < 0.004$), with no significant group-by-treatment interaction ($F = 1.69$, d.f. = 9,135; $P < 0.1$) (*20*). Single degree of freedom contrasts (*21*) revealed that, across all four operative groups, both home-cage and apparatus controls were significantly different from each of the shock groups and that the home-cage controls differed from the apparatus controls ($P < 0.001$).

Table 1. Absolute number of lymphocytes. The data are expressed as $10^{-6}$ cell per milliliter (means ± standard error).

| Treatment | Non-operated | Sham adrenalectomy | Adrenalectomy | Adrenalectomy with pellet |
|---|---|---|---|---|
| Home-cage control | 9.81 ± 1.96 | 8.85 ± 2.17 | 7.41 ± 2.84 | 5.45 ± 1.24 |
| Apparatus control | 8.42 ± 1.50 | 7.93 ± 1.98 | 9.23 ± 2.17 | 6.53 ± 1.52 |
| Low shock | 7.61 ± 1.70 | 6.32 ± 1.80 | 8.01 ± 2.48 | 5.96 ± 1.50 |
| High shock | 6.75 ± 1.99 | 5.02 ± 1.09 | 9.25 ± 2.46 | 5.19 ± 0.74 |

Stress effects on lymphocyte stimulation utilizing a whole blood assay are shown in Fig. 1C. In the nonoperated group there was a progressive suppression of lymphocyte function in response to the stressors, as found in our earlier study. Stress effects on the sham adrenalectomy group and the adrenalectomized animals with steroid replacement were also found. Adrenalectomized animals showed a stress-induced suppression of whole blood lymphocyte stimulation; however, the extent of suppression was less pronounced than in the groups with intact adrenals. ANOVA revealed a highly significant treatment effect ($F = 11.91$, d.f. = 3,135; $P < 0.0001$), group effect ($F = 60.78$, d.f. = 3,135; $P < 0.0001$) and group-by-treatment interaction ($F = 7.44$, d.f. = 9,135; $P < 0.0001$). Since there was a significant group-by-treatment interaction, single degree of freedom comparisons of differences in stress effects among the operative groups were performed. Differences between the home-cage and apparatus controls and between the apparatus controls and each of the shock groups were significantly greater in the animals with intact adrenals than in the two adrenalectomized groups ($P < 0.01$ in all cases).

The results with the whole blood assay, as with the isolated lymphocyte technique, demonstrate that stress-related adrenal secretion of corticosteroids and catecholamines are not required for stress-induced suppression of lymphocyte stimulation. In the whole blood assay, however, animals with functioning adrenals showed greater suppression by each of the stressors than did the adrenalectomized group or the adrenalectomized group with corticosterone pellets. These findings may be related to the retention of the adrenal hormones in the whole blood cultures or to the stress-induced lymphopenia found in the nonoperated and sham adrenalectomy groups.

There were no systematic stress effects on lymphocyte stimulation by PHA in the spleen cell assays (Fig. 1D). ANOVA revealed no significant treatment effect ($F = 1.02$, d.f. = 3,135; not significant), a significant group effect ($F = 5.14$, d.f. = 3,135; $P < 0.002$), and no group-by-treatment interaction ($F = 1.22$, d.f. = 9,135; not significant) (*20*). The lack of a stress-induced suppression of splenic lymphocyte responses to PHA could result from a multiplicity of factors including altered suppressor cell activity or a stress-induced redistribution of PHA-reactive lymphocytes from the peripheral blood to the spleen (*22*).

There is considerable evidence of the modulation of a wide variety of immune parameters by pharmacologic and physiologic doses of corticosteroids (*2–4, 23*). These observations have tended to support the hypothesis that adrenal hormones are the primary mediator of stress effects on the immune system (*4*). The present study demonstrates an adrenal independent mechanism for stress-induced suppression of lymphocyte stimulation by the T cell mitogen PHA in the rat. It may well be that there is an adrenal independent stress-induced depletion of functional subpopulations of T cells or a selective redistribution to lymphoid tissues. A variety of other hormonal and neurosecretory systems may be involved in the adrenal independent stress-induced modulation of T cell function (*24*). Since corticosteroids have differential effects on T and B cell populations (*25*), the role of adrenal hormones

in stress effects on B cell functions must be further investigated. Our findings of adrenal dependent, stress-induced lymphopenia as well as adrenal independent effects on lymphocyte stimulation indicate that stress-induced modulation of immunity is a complex phenomenon involving several, if not multiple, mechanisms.

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20. Adrenal effects unrelated to stress will be described in a separate report.
21. Fisher's protected *t* single degree of freedom contrasts.
22. Radioactivity in the unstimulated cultures for each assay were as follows. For the isolated lymphocyte assay, the counts per minute in the unstimulated cultures across all operative groups were: home-cage control, 935 ± 164; apparatus control, 486 ± 54; low shock, 430 ± 83; high shock, 301 ± 50. For the whole blood assay: home-cage control, 399 ± 38; apparatus control, 209 ± 10; low shock, 184 ± 17; high shock, 189 ± 19. For the spleen cell assay, lower counts were found with the high shock animals only: home-cage control, 1242 ± 145; apparatus control, 1528 ± 187; low shock, 1367 ± 194; high shock, 786 ± 78. The unstimulated cultures in the isolated lymphocyte and whole blood assays were significantly suppressed by the stressful conditions, consistent with our previous study (*1*) in which stress effects were observed in unstimulated cultures.
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## Coupling of Dopamine $D_1$ Recognition Sites with Adenylate Cyclase in Nuclei Accumbens and Caudatus of Schizophrenics

Abstract. *Sodium fluoride, guanylimidodiphosphate, and the $D_1$ dopamine receptor agonist SKF 38393 elicited a greater activation of adenylate cyclase in homogenates of caudate nucleus in schizophrenic than in nonschizophrenic subjects used as controls. Similarly, a greater activation of adenylate cyclase by sodium fluoride was observed in the nucleus accumbens of schizophrenics. These findings suggest that the coupling of dopamine $D_1$ recognition sites with adenylate cyclase is more efficient in the brain of the schizophrenic, presumably because of an increased affinity of the G/F protein for guanosine 5'-triphosphate.*

A hypothesis that has been popular for almost two decades holds that an increased activity of brain dopamine receptors is a neurochemical defect operative in the etiology of schizophrenia (*1–3*). The validity of this hypothesis rests on the finding that the administration of certain dopamine receptor agonists such as amphetamines (*4, 5*) or methylphenidate (*6*) can elicit or exacerbate psychotic symptoms, while dopamine receptor antagonists not only relieve the symptoms of schizophrenia but their potency is proportional to their dopamine receptor blocking activity (*7*). However, there is little direct support for the dopamine hypothesis in the etiology of schizophrenia. In fact, experiments directed to demonstrate a change in the regulation of brain dopamine function in schizophrenia have been inconclusive. Not only the content of dopamine and of its metabolites were found to be similar in various brain areas of schizophrenic (S) and nonschizophrenic (NS) subjects (*8*), but the measurement of dopamine turnover (*9*) and the dopamine-sensitive adenylate cyclase (*10*) in dopamine-rich areas of the brains of S and NS subjects failed to reveal any differences.

The reports supporting a role of dopamine in schizophrenia show that the density of dopamine recognition sites is increased in dopamine-rich areas of S brains (*11–13*). Since the number of dopamine recognition sites is also increased in crude synaptic membranes prepared from the brains of rats that received daily injections of neuroleptics for several weeks (*14*), it is uncertain whether the elevated density of dopamine recognition sites detected in S brains is related to the long-term treatment with neuroleptics or to schizophrenia (*15, 16*).

In order to ascertain whether there is an abnormal dopamine transmission in S brains, we have compared the biochemical properties and the pharmacological profile of the postsynaptic dopamine receptor in dopamine-rich areas of S and NS brains. It is generally agreed that in the corpus striatum, nucleus accumbens, and other dopamine-rich areas of the brain, the postsynaptic recognition sites for dopamine are functionally linked to adenylate cyclase (*17, 18*). This link appears to be regulated by an intrinsic membrane protein, termed G/F protein (*19*). The G/F protein consists of several subunits that have binding sites for guanosine triphosphate (GTP), guanosine diphosphate (GDP), and NaF (*20*). When the dopamine recognition sites are occu-