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Effects of Antipsychotic Drugs on Cellular Immunity in Mice

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The effects of the two antipsychotic drugs, chlorpromazine and haloperidol, the focus of this study, on cell-mediated immunity in male ICR mice. The peripheral blood WBC count decreased significantly in both cholorpromazine and haloperidol. The absolute lymphocyte count decreased only in the haloperidol-treated groups. The absolute number of thy-1-bearing cells described in both the chlorpromazine and haloperidol groups, the most remarkable effects evidencing itrself in the booster groups of higher dosage chlorpromazine (15 mg/kg), and lower and higher-dosage haloperidol (1 mg/kg and 5 mg/kg). The absolute spleen T-lymphocyte count was decreased significantly in the chlorpromazine higher-dosage booster-dose group and the haloperidol higher-dosage (5 mg/kg) single-dose group and the haloperidol lower and higher-dosage (1 mg/kg and 5 mg/kg) booster-dose group. Also, chlorpromazine and haloperidol significantly impaired the in-vitro lymphocyte response to phytohemagglutinin (PHA) and produced a negative reaction of the delayed-hypersensitivity type induced by BCG vaccination. These findings suggest that chlorpromazine and haloperidol suppress the cellular immune responses in mouse.

Key Words: Chlorpromazine, haloperidol, peripheral blood white blood cell (WBC) and lymphocyte count, T-lymphocytes of the thymus and spleen, in-vitro lymphocyte response to PHA, in-vitro study for delayed type of hypersensitivity, male ICR mice.

Since the introduction of neuroleptic drugs for the treatment of psychiatric disorders in the 1950s, significant advances have been made in the understanding of the mechanisms and etiologies of psychosis.
The first report on the treatment of mental illness with chlorpromazine is credited to Delay and Deniker in 1952. They suggested that chlorpromazine produces symptomatic relief of agitation or anxiety and that it could have an ameliorative effect upon psychotic processes with quite diverse symptomatology. Now, chlorpromazine, the prototype of the phenothiazines, is among the most widely used drugs in medical practice. Chlorpromazine and many other related agents have been developed in the last 3 decades, and at the present time there are more than 30 phenothiazine drugs available. Meanwhile, Janssen in Belgium, has found that propriophenones have analgesic effects, but that adding one methylene group to produce a butyrophenone led to quite unexpected neuroleptic effects in animals. The first of these new substances to be made available for clinical use in psychiatry was haloperidol in 1958 (Baldessarini 1980).

Recently, among the new speculations to explain the nature of psychiatric disorders, an association among biomedical genetics, biochemistry, enzymology, virology, and immunology and mental illness has been observed by several investigators (Weiner 1985). As the new field of psychoimmunology has been evolving, some investigators have found evidence of a relationship between psychosocial factors, emotional stress, the central nervous system, and immune function. Solomon *et al.* (1974) have reported that "stress and emotional distress may influence the function of the immunologic system." They have noted that there are considerable data linking personality trait, stress, and failure of defense mechanisms to the onset of autoimmune disease, cancer, and infectious disease. Monjan and Collector

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(1977) have investigated the association between stress and immunity in animals, by observing the effect of a daily auditory stressor for different lengths of time on immune responses of rats. They concluded that "environmental stressors not only can depress immune responsiveness, but can also enhance it."

Since the 1960s, an association between abnormal immune functioning and schizophrenia has been reported by several investigators (Heath and Krupp 1967; Fessel 1962; Stein *et al.* 1976). Although the etiology of altered immunological function in schizophrenia is unknown, several possibilities have been proposed. They include a reaction to virus-like substance in some schizophrenic patients (Torrey *et al.* 1978; Tyrell *et al.* 1979), a manifestation of an autoimmune disease (Health and Krupp 1967), and the result of pharmacological treatment (Knowles *et al.* 1970; Zarrabi *et al.* 1979). Chlorpromazine, especially, has been linked with the appearance of an abnormal lymphocyte in the blood of schizophrenics (Fieve *et al.* 1966). Investigation of the influence of psychotropic drugs on immune function to add to the knowledge of the immuno-psychopharmacology of antipsychotic drugs would seem to be warranted.

In view of this, the author has conducted this controlled animal study.

MATERIALS AND METHODS

Male ICR mince, 6 to 8 weeks old, and weighing approximately 20 mg, and chlorpromazine (Smith Kleine and French Lab.) or haloperidol (Janssen Pharm.) for the drug treatment and saline for the control, were used. The drugs and the saline were administered intraperitoneally.

A major subgroup of the mice were given drugs and the rest, the control group, were given saline. A subgroup of the mice given drugs were given chlorpromazine, and the rest of those given drugs was given haloperidol. A subgroup of each of these two groups given specific drugs were given a lower doses of the drug allotted to them, and the remainder of each of these two groups given specific drugs were given a higher dose of the drug allotted to them. A subgroup of each of the five groups, the control group and the four subgroups treated with drugs, were given a booster dose of the group at the end of a specified length of time following the giving of the single original dose. The single and booster injections of saline were 0.2 ml respectively. The lower doses of chlorpromazine and haloperidol were 5 mg/kg and 1 mg/kg respectively, and the higher doses, 15 mg/kg and 5 mg/kg, respectively. The mice which were given single doses only, whether it was of the saline are either of the drugs, were sacrificed 48 hours following the administration of that one dose; the mice which were given a booster dose as well as an original dose were sacrificed 72 hours following the administration of the booster dose.

Samples of one to two ml of blood were taken from the retro-orbital plexus just before the sacrifices and prepared as direct smears. A total white blood cell count was done, and lymphocytes were enumerated by a differential white blood cell count under the light microscope in each case.

The thymus and spleen were removed from each mouse aseptically, and a cell suspension was made of them using the method which Mishell *et al.* (1980) has used. Isolating the mononuclear cells from the thymus-cell suspension by means of the procedure used by Kim *et al.* (1977), the suspension was centrifuged at 400×g for 30 minutes on a Ficoll-Hypaque gradient, which was composed of 9% Ficoll (Sigma Co.) and 33.9% Hypaque (Winthrop Lab.). Next, a lymphocyte suspension with $5-6\times10^6$ cells/ml was made by centrifuge at 200×g for 10 minutes and washing in Hank's solution (Gibco.). The spleen cell suspension was layered with lymphoprep (Nyegaard & Co.) and centrifuged at 400×g for 30 minutes, following which a lymphocyte-cell suspension with $5-6\times10^6$ cells/ml was made by centrifugation at 400×g for 20 minutes and washing in phosphate-buffered saline (PBS) (Gibco.)

Using Golub's method the thy-l-bearing cells of the thymus and the T-lymphocytes of the spleen were identified by direct immunofluorescence with rabbit-anti-mouse-brain (C3H)-adsorbed, fluorescein-izothiocyanate-conjugated (Bionetics) reagent. The rabbit-anti-mouse-brain serum was stored at −20°C as separate aliquots, and diluted as a range of 1/20 by adding PBS (pH 7.2), containing 5% fetal bovine serum (Gibco.). Five μl of diluted rabbit-anti-mouse-brain serum was added to the 50 μl of lymphocyte suspension ($5-6\times10^6$ cells/ml) on a slide. The slide was then incubated at room temperature (20–25°C) for 30 minutes, and examined at 450× with a Fluorestar microscope (American Optical) for presence of peripheral apple-green-stained T-cells.

Lymphocyte transformation was measured by means of method used by Webel *et al.* (1975). The lymphocyte cells of the spleen were suspended with RPMI 1640 (Gibco), containing 20% fetal calf serum (Gibco), penicillin G 100 units/ml, and streptomycin 100 μg/ml. Aliquots of 200 μl (5×10^6 cells/ml) of the mixture were placed in a separate well of a

microculture plate (Flow Lab.), and to each was added 10 μl of PHA (1,000 μl). Culture plates were sealed and incubated for 72 hours in 5% CO_2 at 37°C. All procedures were performed 3 times under sterile conditions. Following incubation, the cultures were labelled with 1 μCi of 3H-thymidine (New England Nulcear) and incubated again, this time for 4 hours. Following this period of incubation, they were harvested, using a glass-fiber filter paper (Grade 934 AH, Reeve Angel). The activity of the samples was then determined, with the use of a Packard liquid scintillation β-counter. The mean of the triplicate determination was calculated. The data were expressed as counts per minute (CPM) in the stimulated cultures minus the CPM in the unstimulated cultures (ΔCPM).

In an in-vivo study of delayed-type hypersensitivity, overall T-lymphocyte function was assessed through doing tuberculin tests after BCG vaccinations. The test group was divided into two groups: a BCG-immunized group and a non-immunized group. In the BCG-immunized group, all mice were immunized with an intraperitoneal injection of 0.1 ml of BCG-Y-strain suspension (10^8/ml). In the non-immunized group, all of the mice were injected with saline (0.1 ml) intraperitoneally. Then saline (0.2 ml), chlorpromazine (15 mg/kg), or haloperidol (5 mg/kg) was injected intraperitoneally on days 3, 6, 9, 12, 15, 18, 21 and 24 after BCG vaccination. Four weeks later, all mice were challenged with 0.03 ml of PPD (5 TU/0.1ml) injected intradermally into the footpad of each mouse, and the thickness of the footpad was measured with a dial thickness gauge (Mitutoyo MFG Co. Ltd.) 0, 24, 48 and 72 hours later.

RESULTS

In Table 1 it is shown that the white blood cell count was decreased significantly in all of the chlorpromazine groups compared with the control groups ($p<.01$, $p<.001$, $p<.01$, $p<.001$). The white blood cell count of the 15 mg/kg booster group, especially was decreased more significantly than the same dose single group ($p<.001$). The absolute lymphocyte count that was decreased, but not significantly. In Table 1, also, it can be seen in all of the haloperidol groups, the WBC count was decreased significantly ($p<.01$, $p<.001$, $p<.05$, $p<.001$). Generally, the decreasing of the WBC count was more marked in the booster-dose groups than in the single-dose groups. Also, it can be observed that absolute lymphocyte count was decreased significantly in all of the haloperidol groups compared with the control groups ($p<.01$, $p<.01$, $p<.01$, $p<.05$).

Table 1. Effects of chlorpromazine and haloperidol on the differential count of lymphocyte in mouse peripheral blood

Group	N	WBC/mm³*	Lymphocyte(%)*
Control (Saline)			
single	10	7080±175	72±12
booster	10	7075±218	71±12
Chlorpromazine (5mg/kg)			
single	9	5983±518[a]	67±9
booster	10	5783±390[b]	62±9
Chlorpromazine (15mg/kg)			
single	9	6644±445[a]	68±11
booster	9	5533±436[b,c]	64±12
Haloperidol (1mg/kg)			
single	9	6590±388[a]	58±5[a]
booster	9	6065±289[b,d]	57±6[a]
Haloperidol (5mg/kg)			
single	10	6873±202[e,f]	61±8[a]
booster	10	5900±285[b,g]	60±7

* Mean ± S.D.

[a] $p<.01$, comparing with control single, or booster group

[b] $p<.001$, comparing with control booster group

[c] $p<.001$, comparing with chlorpromazine (15mg/kg) single group

[d] $p<.01$, comparing with haloperidol (1mg/kg) single group

[e] $p<.05$, comparing with control single, or booster group

[f] $p<.001$, comparing with haloperidol (1mg/kg) booster group

[g] $p<.001$, comparing with haloperidol (1mg/kg) single group, or haloperidol (5mg/kg) single group

In all of the chlorpromazine groups, the absolute number of thy-l-bearing cells was decreased significantly ($p<.001$, $p<.05$, $p<.001$, $p<.01$), this decrease being most noticeable in the 15 mg/kg booster group (Table 2). Also, in all of the haloperidol groups, the absolute thy-l-bearing cell count was decreased significantly ($p<.001$, $p<.01$, $p<.001$, $p<.001$) (Table 2). Generally, the decrease in the absolute thy-l-bearing cell count was more obvious in the booster-dose groups than in the single-dose groups.

Table 2. Effects of chlorpromazine and haloperidol on thy-l-bearing cell in mouse thymus

Group	N	Thy-l-bearing cell (%)*
Control (Saline)		
single	11	90.8±7.0
booster	10	90.1±6.3
Chlorpromazine (5mg/kg)		
single	10	78.1±16.0[a]
booster	10	78.9±13.7[b]
Chlorpromazine (15mg/kg)		
single	11	71.6±8.3[b]
booster	10	60.1±7.3[ac]
Haloperidol (1mg/kg)		
single	10	68.0±6.6[a]
booster	10	55.6±8.9[ad]
Haloperidol (5mg/kg)		
single	9	53.9±7.5[ac]
booster	10	49.6±6.1[ac]

* Mean ± S.D.
[a]p<.001, comparing with control single, or booster group
[b]p<.05, comparing with control booster group
[c]p<.01, comparing with chlorpromazine (5mg/kg) single, or booster group
[d]p<.01, comparing with haloperidol (1mg/kg) single group
[e]p<.001, comparing with haloperidol (1mg/kg) single group

Table 3. Effects of chlorpromazine and haloperidol on T-lymphocyte subpopulation in mouse spleen

Group	N	T-lymphocyte (%)
Control (Saline)		
single	10	28.4±8.0
booster	9	28.8±7.1
Chlorpromazine (5mg/kg)		
single	9	27.1±8.6
booster	10	24.2±8.0
Chlorpromazine (15mg/kg)		
single	10	22.6±8.9
booster	9	16.5±6.4[ab]
Haloperidol (1mg/kg)		
single	9	25.6±8.8
booster	10	18.9±5.0[a]
Haloperidol (5mg/kg)		
single	10	14.2±8.1[ac]
booster	10	19.5±4.3[a]

* Mean ± S.D.
[a]p<.01, comparing with control single, or booster group
[b]p<.01, comparing with chlorpromazine (5mg/kg) single, or booster group
[c]p<.01 comparing with haloperidol (1mg/kg) single group

As can be seen in Table 3, only in the 15 mg/kg booster-dose group of mice treated with chlorpromazine, was the absolute number of T-cells decreased significantly compared with the control, or the 5 mg/kg single-dose or booster-dose group (p<.01). Also, the absolute spleen T-cell count was decreased significantly in all of the haloperidol groups except in the 1 mg/kg single-dose group (p<.01, p<.01, p<.01).

In all of the chlorpromazine-treated group, ^{3}H-thymidine uptake was suppressed significantly (p<.05, p<.05, p<.05, p<.01) (Table 4). Generally, the suppressing of ^{3}H-thymidine uptake was more emphasized in the high-dose groups than in the low-dose groups. In all of the haloperidol-treated groups, ^{3}H-thymidine uptake was susppressed significantly (p<.05, p<.05, p<.05, p<.05 (Table 4). In the 5 mg/kg booster-dose group this suppressing effect was more prominent than the 1 mg/kg single-dose group of mice trated with haloperidol.

Figure 1 shows that both chlorpromazine and haloperidol treatment produced a negative tuberculin reaction in the immunized mouse, while in the control group the reaction was positive. However, in the non-immunized mouse, as seen in Figure 2, the results of the tuberculin test were nagative in all groups.

Table 4. Effects of chlorpromazine and haloperidol on PHA stimulated lymphocyte transformation

Group	N	^{3}H-thymidine uptake (cpm/culture)*
Control (Saline)		
single	9	5057±2112
booster	9	4934±2001
Chlorpromazine (5mg/kg)		
single	9	3558±1163[a]
booster	9	3320±1107[a]
Chlorpromazine (15mg/kg)		
single	9	2158± 918[ab]
booster	9	1985±1003[ab]
Haloperidol (1mg/kg)		
single	8	3545±1152[a]
booster	9	2848±1048[a]
Haloperidol (5mg/kg)		
single	8	2530±1003[a]
booster	8	2318± 987[ac]

* Mean±S.D. [^{3}H-thymidine uptake expressed as (cpm with mitogen)-(cpm without mitogen)]
[a]p<.05, comparing with control single, or booster group
[b]p<.01, comparing with chlorpromazine (5mg/kg) single, or booster group
[c]p<.05, comparing with haloperidol (1mg/kg) single group

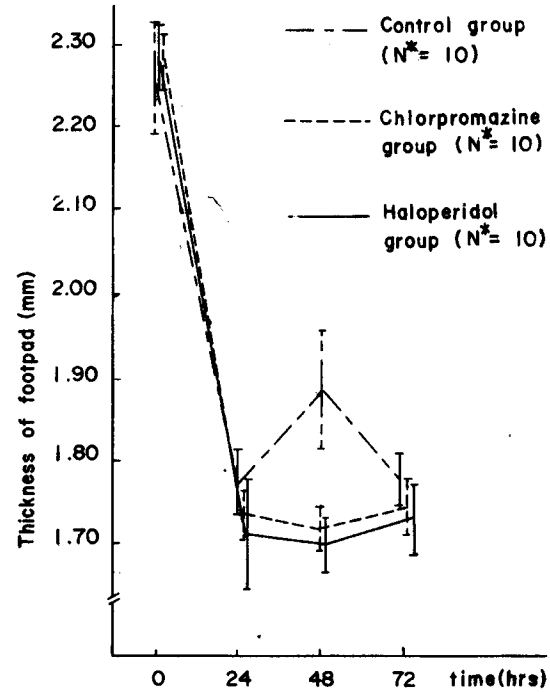

Fig. 1. Effects of chlorpromazine and haloperidol on tuberculin reaction of BCG immunized mouse (Mean±S.D.)
**N = numbler of animals used*

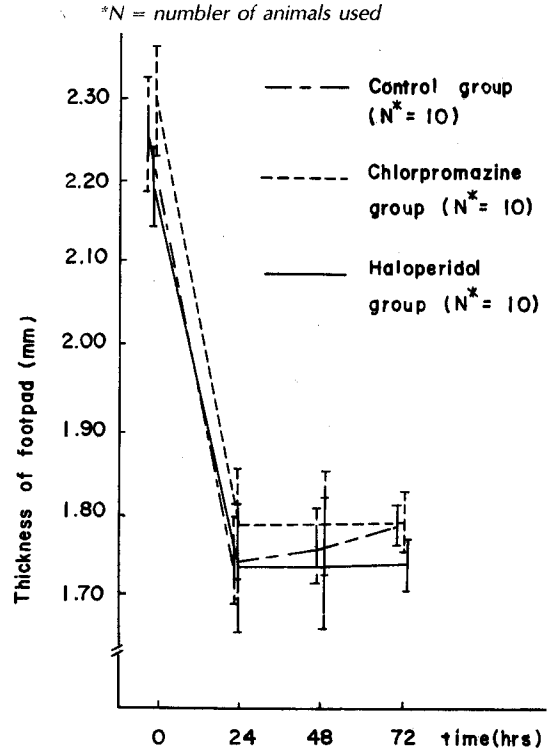

Fig. 2. Effects of chlorpromazine and haloperidol on tuberculin reaction of non-immunized mouse (Mean±S.D.)
**N = number of animals used*

DISCUSSION

These results show that chlorpromazine and haloperidol inhibit the cellular-immune response of the mouse. Both chlorpromazine and haloperidol produced a significant decrease in the absolute number of thy-l-bearing cells and impaired the in-vitro lymphocyte response to PHA. Also, both drugs suppressed the delayed-type hypersensitivity reaction.

Recently, it has become known that psychotropic drugs effect the immune system. That neuroleptics affect the immune system is supported by several lines of evidence. First, chlorpromazine has been linked to

the presence of abnormal lymphocytes in the blood of schizophrenic patients (Fieve *et al.* 1966). The authors that carefully done study concluded that the increased number of atypical lymphocytes observed in schizophrenia was related to phenothiazine therapy, and that there was no primary disturbance of the lymphocytes. Second, chlorpromazine may be related to the development of systemic lupus erythematosis as an immune complex disorder (Fessel and Solomon 1960; Dubois *et al.* 1972). Third, antinuclear antibodies have also been associated with long-term neuroleptic treatment (Zarrabi *et al.* 1979; Johnstone and Whaley 1975). Antinuclear-factor incidence is also reported increased in schizophrenia (Fessel 1962). They may be related to the high incidence of psychosis in conjunction with systemic lupus erythematosis, an autoimmune disease associated with antinuclear antibodies (Fessel and Solomon 1960). Fourth, chlorpromazine may be associated with the suppression of antibody production and a suppressive effect of neuroleptics on lymphocyte responsiveness (Knowles *et al.* 1970; Zarrabi *et al.* 1979). Knowles *et al.* (1970) investigated the lymphocyte transformation using PHA-M in treated and untreated schizophrenia and compared the results with normal controls. They speculated that the actual mechanism of the impaired PHA-induced transformation of treated schizophrenic lymphocytes may be due either to reduced lymphocyte viability or to a chemical change in the lymphocyte membrane, and concluded that lymphocyte abnormalities in schizophrenia may be drug-induced and that there is no primary lymphocyte disorder. Fifth, Delsi *et al.* (1981), using an immunofluorescent antibody technique have quantified immunoglobulin (Ig): IgG, IgA, and IgM in cerebrospinal fluid and plasma taken from 35 chronic schizophrenic patients and controls. They observed generalized reduction in Ig levels in schizophrenic patients compared with controls, and reported that their results may be consistent with the notion that neuroleptic medication may suppress the immune response, but the etiology of these findings was elusive. Finally, Zarrabi *et al.* (1979) reported that the percentage of T-lymphocytes was below normal in 13 of 41 patients treated with chlorpromazine. For the authors, speculating that the mechanism of action of chlorpromazine may be related to a direct effect on suppressor or helper T-lymphocytes, leading to an increased production of IgM by B-lymphocytes, is tempting.

In this study, chlorpromazine and haloperidol produced a significant decrease in the absolute number of thy-l-bearing cells of the thymus, and impaired the in-vitro lymphocyte response to PHA and the delayed-type hypersensitivity. With these findings, it is concluded that chlorpromazine and haloperidol inhibit the cellular-immune response of the mouse. The action mechanisms of these findings can be speculated to explain some aspects of the endocrine functions of neuroleptics. The effects of neuroleptic drugs on hypothalamic regulatory hormones result in profound changes in the endocrine system. Chlorpromazine can reduce gonadotropins, as well as those of estrogens and progestins, and increase the secretion of prolactin. Among these endocrine changes, the increase in the secretion of prolactin is the greatest one. Chlorpromazine and haloperidol inhibit dopaminergic transmission by blocking dopamine receptors and raise serum prolactin concentrations. This effect is brought about through either suppression of the hypothalamic prolactin-inhibitory factor or antagonism of that factor at the level of the pituitary, or both (De La Feunte and Rosenbaum 1981).

Meanwhile, there have been reports of a reduced life span among schizophrenic patients (Tsuang and Woolson 1977). Two major categories of illness that conceivably would shorten the life span of a population and could be associated with reduced immune responsiveness are infections and neoplasms. Also, some studies of schizophrenic patients, treated with neuroleptics, report a relative rise in the incidence of cancer which may be related to a rise in prolactin levels induced by neuroleptic drugs (Salih *et al.* 1972; Ettigi *et al.* 1973). In laboratory animals, prolactin is a factor in the growth of some mammary carcinomas. Dimethyl-benzanthracene-induced mammary carcinoma in Sprague-Dawley rats is prolactin-dependent tumor (Nagasawa and Yanai 1970). Also, Boot (1970) considered prolactin to be the hormone most directly responsible for mammary tumor formation in mice. Since breast cancer seems to be responsive to prolactin suppression in some patients, the use of drugs known to increase prolactin production might be associated with exacerbation of this disease. Therefore, some of the drugs known to stimulate prolactin including chlorpromazine or haloperidol, may be contraindicated in patients whose breast cancers show prolactin dependence (Hilf *et al.* 1971; Palmer and Maurer 1972; Salih *et al.* 1972).

In the light of these findings, it is concluded that chlorpromazine and haloperidol suppress cellular immune response in mice, and discussed about the possible association between neuroleptics, impaired immune responses and prolactin. But the interpretation of these findings remains largely speculative. Thus, further investigation along these lines is indicated.

CONCLUSION

The findings of this experimental study are summarized as follows:

1) Both chlorpromazine and haloperidol produced a significant decrease in the peripheral blood WBC count, but only haloperidol produced a significant decrease in the absolute lymphocyte count.

2) Both chlorpromazine and haloperidol produced a significant decrease in the absolute number of thy-l-bearing cells. This effect was more remarkable in the booster groups of both drugs.

3) In the chlorpromazine booster group of 15 mg/kg, the haloperidol booster group of 1 mg/kg, and haloperidol single and booster groups of 5 mg/kg, the absolute spleen T-lymphocyte count was decreased significantly compared with the control group.

4) In all of the drug-treated groups, chlorpromazine and haloperidol impaired the in-vitro lymphocyte response to PHA.

5) In all of the drug-treated groups, the PPD skin test following BCG vaccination was negative. Therefore, both drugs suppressed the delayed-type hypersensitivity reaction.

With this evidence, it is concluded that chlorpromazine and haloperidol inhibit cellular-immune response in mice.

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