The Effects of Subcutaneous Injections of Glucocorticoids on Amoeboid Microglia in Postnatal Rats*

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Received July 4, 1994

Summary. Subcutaneous injections of glucocorticoids into postnatal rats resulted in a drastic reduction in the number of amoeboid microglial cells in the corpus callosum as shown by their labelling with the monoclonal antibodies of the OX-series, ED1, lectin and rhodamine isothiocynate (RhIc). In rats receiving 2 or 3 injections of glucocorticoids and killed at the age of 4 or 7 days, between 40 to 60% of the callosal amoeboid microglial cells were depleted when compared with the corresponding control animals. The cells that survived the glucocorticoid treatments became ramified, while those in the controls of the same age group remained round or amoeboidic. In rats killed at 2 or 3 weeks of age, the microglia became extremely ramified with a concomitant diminution in their immunostaining, particularly in the glucocorticoid-injected rats. In rats receiving glucocorticoid injections along with RhIc, the RhIc-laden amoeboid microglia appeared round and amoeboidic and were intensely stained with OX-42, suggesting their activation and upregulation of complement type 3 receptors when compared with rats receiving only glucocorticoids. Compared with the control, cellular proliferation continued in rats given glucocorticoid injection as indicated by the occurrence of many bromodeoxyuridine-labelled cells in the corpus callosum at the age of 6 days. Ultrastructural studies confirmed the presence of mitotic cells identified as amoeboid microglia because of their labelling with isolectin. A striking ultrastructural feature in glucocorticoids-injected rats was the wide occurrence of amoeboid microglial cells that had ingested a variable number of lectin-labelled cells.

It is concluded from this study that the drastic reduction of amoeboid microglia after glucocorticoid injections can be attributed to the suppression of their precursor cells, monocytes. Another possible explanation is the acceleration of their degeneration process, probably greatly enhanced by glucocorticoids; the degenerating amoeboid microglia were readily eliminated by the surviving amoeboid microglial cells through endocytosis. Glucocorticoids also accelerated the maturation process of the persisting amoeboid microglia to become ramified in form.

It has been well established that amoeboid microglial cells (AMC) in the developing rat brain are active macrophages (LING and TAN, 1974; MATSUMOTO and IKUTA, 1985) probably derived from circulating monocytes which infiltrate the nervous tissue in the early postnatal period (LING, 1981; LING and WONG, 1993). These cells are present transiently in the postnatal rat brain; by about the second postnatal week they transform into the ramified microglial cells which persist through adulthood (KAUR et al., 1985; KAUR and LING, 1991). Immunocytochemical studies have shown that, just like monocytes and their derivative macrophages, AMC display type 3 complement receptors (CR3) and major histocompatibility complex (MHC) class I and II antigens (LING et al., 1990, 1991), especially when challenged with the bacterial toxin, lipopolysaccharide (XU and LING, 1994). A previous study (LING, 1982) reported that the large accumulation of these brain macrophages in the corpus callosum in postnatal rats was greatly reduced when cortisone was administered subcutaneously. The response of AMC to cortisone is consistent with the finding of RUSSO-MARIE (1992) in respect to the effect of glucocorticoids which are known to suppress the

*This study was supported by a research grant (RP 920365) from the National University of Singapore and a grant (NSC-75-0412-B002-12) from the National Taiwan University.
number of circulating monocytes, thereby leading to a consequential reduction in the number of tissue macrophages. The present study was undertaken to find out whether the proliferative capability and surface antigens/receptors constitutively expressed on amoeboid microglia would be affected following the administration of glucocorticoids. Another aspect to be explored was the effect of glucocorticoids on the phagocytic activity of these cells, which are known to avidly endocytose the fluorescent dye rhodamine isothiocyanate (Rhlc) when injected intravenously or intraperitoneally into postnatal rats (Xu et al., 1993). These data would be vital in a better understanding of the functional roles of AMC.

MATERIALS AND METHODS

Injection of glucocorticoids

Wistar rats aged 1 day were used in this study. They were divided into two separate groups receiving dexamethasone and cortisone injections, respectively. Two different types of glucocorticoids were used to assess their differential effects, if any, on the development of AMC. The rats in Group I received 3 single subcutaneous injections of 30 μl dexamethasone (200 μg dissolved in 0.5ml of olive oil equivalent to 1 mg/kg body weight) at the dorsum of the neck at 1, 3 and 5 days of age. The corresponding control rats were given an equal dosage and frequency of subcutaneous injections of olive oil. The rats were sacrificed at 4, 7, 14 and 21 days of age (The rats killed at the first survival interval received only 2 injections). At least 4 rats were sacrificed in each age group.

Injection of rhodamine isothiocyanate (Rhlc)

To ascertain the phagocytic activity of AMC following glucocorticoid treatment, some of the dexamethasone-injected rats and their controls were given a single intraperitoneal injection of 50 μl 1% Rhlc (Sigma Co.) in normal saline on the 5th day. They were killed at 7, 14 and 21 days of age.

Injection of bromodeoxyuridine

To determine the mitotic activity of AMC, 2 of the dexamethasone-injected rats and their corresponding controls were given a single intraperitoneal injection of 50 μl bromodeoxyuridine (Sigma Co.) dissolved in saline (10 mg/ml) on the 5th day. The rats were killed at 6 days of age.

Group II rats were given a single subcutaneous injection of cortisone (Sigma Co.) (5 mg in 0.1 ml of saline at 1 day of age) and were killed at 4, 7 and 14 days. Some animals were given an additional injection of cortisone at 3 days of age, but none of them survived.

Perfusion and tissue processing

For immunohistochemistry, the rats were perfused under ether anaesthesia with Ringer's solution followed by an aldehyde fixative composed of a mixture of periodate-lysine-paraformaldehyde with a concent-

Fig. 1. Large numbers of OX-42 immunoreactive amoeboid microglial cells in the corpus callosum in a control rat receiving olive oil injections and killed at the age of 4 days. ×110

Fig. 2. Drastic reduction of OX-42 immunoreactive cells in the corpus callosum in a dexamethasone-injected rat killed at the age of 4 days. ×110
tration of 2% paraformaldehyde, according to the method by McLEAN and NAKANE (1974). After perfusion the brains were removed and fixed in a similar fixative for another 2 h, after which they were kept in 0.1 M phosphate buffer containing 10% sucrose overnight at 4°C. Frozen coronal sections of the brains were cut at the level of the optic chiasma at 40 μm thickness and rinsed in phosphate buffered saline (PBS). The sections were then incubated with one of the following monoclonal antibodies: OX-42 (Sera Lab, MAS 370b), OX-18 (Sera Lab, MAS 101b), OX-6 (Sera Lab, MAS 043b) diluted 1:100 with PBS and ED1 (Serotec, MCA 341) diluted 1:400 with PBS. These antibodies recognise complement type 3 (CR3) receptors, major histocompatibility class I and II antigens and cells of the monocyte/macrophage lineage, respectively. Incubation time with the above antibodies was between 18 and 24 h at room temperature. Subsequent antibody detection was carried out using the Vectastain ABC-kit (PK-4002, Vector Laboratories,

Fig. 3. Amoeboid microglial cells in the corpus callosum in a control rat receiving olive oil injections and killed at the age of 7 days. The cells are intensely immunoreactive with OX-42. Most of the labelled cells are round and amoeboidic with some showing short stout projections. ×340

Fig. 4. OX-42 immunoreactive microglial cells in the corpus callosum in a dexamethasone-injected rat killed at the age of 7 days. Note the extensive ramification of the labelled cells when compared with those of the corresponding control rat (Fig. 3). ×340

Fig. 5. Highly branched OX-42 immunoreactive cells in the corpus callosum of a 2-week-old control rat receiving olive oil injections. ×340

Fig. 6. Highly branched OX-42 immunoreactive cells in the corpus callosum of a 2-week-old rat receiving dexamethasone injections. ×340
Burlingame, CA) against mouse IgG with 3,3'-diaminobenzidine (DAB, Sigma 5637) as a peroxidase substrate and intensified with nickel ammonium sulphate.

Three animals each from the 4- and 7-day-old dexamethasone-injected rat groups were used for quantitative study. For comparison, equal number of rats from the control group were also studied. OX-42 positive cells were enumerated in the supraventricular corpus callosum using an ocular grid measuring 0.0125 mm². A total area of 0.25 mm² was examined in each rat.

In rats receiving dexamethasone and RhIc injections and their corresponding controls, coronal frozen sections of the brain of a 30 μm thickness were cut and mounted on gelatinised slides, air dried and coverslipped with the nonfluorescent medium, Entellan (Merck, Darmstadt, Germany). The sections were examined and photographed in a Leitz Aristoplan photomicroscope equipped with a mercury lamp for fluorescence microscopy using a wide band ultraviolet excitation filter (excitation range 515-560 nm). Adjacent serial sections were incubated with the antibody OX-42 and processed as described above.

Sections from brains of rats which had received injections of dexamethasone and bromodeoxyuridine and their corresponding controls were incubated with the antibody antibromodeoxyuridine (Amersham) with a concentration of 1:1 according to the method of SVENSSON (1993). Adjacent serial sections were incubated with OX-42 and were processed as described above for other antibodies.

For lectin histochemistry, the rats were perfused with a mixed aldehyde solution composed of 2% paraformaldehyde and 2.5% glutaraldehyde in 0.1 M cacodylate buffer, pH 7.4. After perfusion, which lasted for 10 min, the brain was removed and post-fixed in a similar fixative for 8 h at 4°C. The cerebrum at the level of the optic chiasma was cut serially with a vibratome into coronal sections 30 or 60 μm thick. In order to exclude the staining of endogenous peroxidase in lysosomes, the sections were preincubated in 0.5% H₂O₂ for half an hour before the application of the lectin. After a brief pre-washing with 0.1 M cacodylate buffer, free-floating sections were incubated in a lectin solution of Griffonia simplicifolia conjugated with horseradish peroxidase (GSA I-B4-HRP) (Sigma, L5391; 0.025 mg/ml of 0.05 M Tris buffer saline, pH 7.4, with 0.1% Triton X-100) overnight at 4°C. Following the incubation, the sections were reacted with diaminobenzidine. For light microscopy, 30 μm thick sections treated with lectin were then collected on slides and counterstained with 0.5% thionine. For electron microscopy, 60 μm thick lectin-treated sections were postfixed in 1% osmium tetroxide in 0.1 M cacodylate buffer. The sections were then dehydrated in a graded series of alcohol and embedded in Eraldite mixture. Ultrathin sections were double stained with lead citrate and uranyl acetate and examined in a JEOL 1200 EX electron microscope.

**OBSERVATIONS**

All rats receiving multiple subcutaneous injections of dexamethasone appeared physically active, although their body sizes tended to be smaller when compared with the controls. Rats receiving a single injection of cortisone, on the other hand, appeared rather lethargic and did not survive beyond 14 days of age.

**Immunohistochemistry**

The most remarkable feature in rats receiving dexamethasone injections and killed at the age of 4 or 7 days was the drastic reduction in the number of OX-42 immunoreactive AMC in the corpus callosum when compared with that of the corresponding control animals (Figs. 1, 2 and Table 1). In 7-day-old rats, a majority of the OX-42 immunoreactive cells in the control rats displayed fine branching processes; the intensity of immunoreactivity of these cells was noticeably reduced (Fig. 5). In dexamethasone-treated animals, the immunoreactivity of the extremely ramified OX-42 positive cells was further attenuated (Fig. 6).

The results with OX-18 concurred with those for OX-42. In rats killed at the age of 4 or 7 days, the number of OX-18 positive cells in the experimental rats was reduced when compared with that of the control rats (Figs. 7, 8). Most of the labelled cells in the dexamethasone-injected animals were oval, elongated or ramified, distinct from those in the control animals in which the round and oval cells prevailed.

<table>
<thead>
<tr>
<th>Age of rat</th>
<th>Dexamethasone-injected rat OX-42 (mean ± SD)</th>
<th>Control rat OX-42 (mean ± SD)</th>
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<tr>
<td>4 days (n=3)</td>
<td>187.66 ± 4.73</td>
<td>345.0 ± 8.88</td>
</tr>
<tr>
<td>7 days (n=3)</td>
<td>242.33 ± 9.07</td>
<td>560.33 ± 10.21</td>
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Fig. 7. A large number of OX-18 immunoreactive cells in the corpus callosum in a control rat receiving olive oil injections and killed at the age of 4 days. ×110

Fig. 8. A few OX-18 immunoreactive cells in the corpus callosum in a dexamethasone-injected rat killed at the age of 4 days. ×110

Fig. 9. RhIC-labelled amoeboid microglial cells in the corpus callosum in a control rat receiving subcutaneous injections of olive oil and an intraperitoneal injection of RhIC and killed at the age of 7 days. ×140

Fig. 10. Corpus callosum in a dexamethasone-injected rat receiving an intraperitoneal injection of RhIC and killed at the age of 7 days. Note the drastic reduction in the number of RhIC-labelled cells when compared with that of the corresponding control rats (Fig. 9). The persisting RhIC-labelled cells, however, show an intense fluorescence labelling. ×140

Fig. 11. Serial adjacent section to Figure 10, immunostained with OX-42. Note that the immunoreactive cells remain round and amoeboidic and display more intense immunoreactivity when compared with those in rats treated with dexamethasone alone (see Fig. 12). ×140

Fig. 12. OX-42 positive cells in the corpus callosum of a 7-day old dexamethasone-injected rat. ×140
The immunoreactivity of the labelled cells also diminished with dexamethasone treatment. In rats killed at 2 and 3 weeks of age, the difference between both the control and experimental groups became less obvious because the immunostained cells were hardly detectable.

The immunoreactivity of AMC with OX-42 and OX-18 in cortisone-injected rats was comparable to that of dexamethasone-injected rats up to 2 weeks of age. The cortisone-injected rats did not survive beyond 2 weeks of age.

OX-6 positive cells were absent in the corpus callosum in the control group and rats treated with dexamethasone or cortisone at all the age.

A quantitative study showed that the number of OX-42 positive cells in the corpus callosum in 4- and 7-day-old rats was reduced drastically in the dexamethasone-injected rats when compared to the control rats (Table 1). The reduction was between 50-60%.

**Rhodamine injection**

In control rats receiving a single intraperitoneal injection of RhIc and killed at the age of 7 days, a large number of round AMC emitting bright fluorescence were observed in the corpus callosum (Fig. 9). In the corresponding experimental rats given dexamethasone injections, the number of RhIc-labelled cells was considerably reduced (Fig. 10). This was particularly evident in rats killed at the age of 7 days (Fig. 10). In longer surviving rats, i.e. those killed at 2 and 3 weeks of age, the RhIc-labelled cells became

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**Fig. 13.** A large number of ED1 positive cells in the corpus callosum in a control rat receiving olive oil injections and killed at the age of 7 days. ×340

**Fig. 14.** ED1 positive cells are markedly reduced in the corpus callosum in a dexamethasone-injected rat killed at the age of 7 days; the cells are extremely ramified with long extending processes. ×340

**Fig. 15.** A large number of bromodeoxyuridine-labelled cells (dense dots) in the corpus callosum in a control rat which had been injected with olive oil and killed at the age of 6 days. ×340

**Fig. 16.** Widely distributed bromodeoxyuridine-labelled cells (dense dots) in the corpus callosum in a dexamethasone-injected rat killed at the age of 6 days. ×340
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oval or elongated and ramified. An interesting feature of the RhIC-labelled AMC in dexamethasone-treated rats killed at the age of 7 days was that the cells appeared round and amoeboidic (Fig. 11). This is clearly distinct from the extreme ramifications of OX-42 AMC in dexamethasone-injected rats that were not labelled with RhIC (Fig. 12). Furthermore, these AMC displayed a more intense immunoreactivity (Fig. 11) than those not loaded with RhIC (Fig. 12). In longer survival periods, the OX-42 positive cells became ramified with a diminution of immunoreactivity.

**ED1 and bromodeoxyuridine labelling**

Results with ED1 labelling paralleled those with OX-42. The labelled cells in the corpus callosum in control rats were round and closely packed (Fig. 13). Following glucocorticoid injection, the labelled cells were dramatically reduced and ramified (Fig. 14). Bromodeoxyuridine labelled cells were observed in the corpus callosum in both the control and glucocorticoid-injected rats, although there were fewer labelled cells in the latter animal group (Figs. 15, 16). Adjacent sections stained with OX-42 showed a

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*Fig. 17.* A large number of lectin-labelled amoeboid microglial cells in the corpus callosum of a control rat receiving saline injection and killed at the age of 4 days. ×100

*Fig. 18.* Very few lectin-labelled amoeboid microglial cells are observed in the corpus callosum of a rat receiving a cortisone injection and killed at the age of 4 days (compare with the corresponding control rat in Fig. 17). ×100

*Fig. 19.* A large number of lectin-labelled round amoeboid microglial cells in the corpus callosum of a control rat receiving a saline injection and killed at the age of 7 days. ×100

*Fig. 20.* Elongated and ramified lectin-labelled microglial cells in the corpus callosum of a rat receiving a cortisone injection and killed at the age of 7 days (compare with the corresponding control in Fig. 19). ×100
Fig. 21. A lectin-labelled amoeboid microglial cell in the corpus callosum of a 4 day-old rat receiving a cortisone injection. The cell has engulfed three degenerating cells which are also lectin labelled at their membranes (arrows). G Golgi apparatus. ×9,000

Fig. 22. Corpus callosum of a 4 day-old rat receiving a cortisone injection. A mitotic amoeboid microglial cell containing lysosomes (Ly) is labelled with isolectin at its plasma membrane. ×7,400
reduction in the OX-42 positive cells in the glucocorticoids-injected rats when compared to the control rats.

Lectin labelling

With GSA I-B4, labelled AMC were markedly reduced in rats given cortisone injections and killed at the age of 4 days (Figs. 17, 18). In cortisone-injected rats killed at the age of 7 days, all the lectin-labelled cells had become ramified, while in the corresponding control rats, the labelled cells remained round and amoeboidic (Figs. 19, 20). The results in dexamethasone-injected rats were similar to those of cortisone-injected rats.

A striking ultrastructural feature of cortisone or dexamethasone-injected rats was the common occurrence of lectin-labelled AMC that had endocytosed a variable number of degenerating cells labelled by the isolectin (Fig. 21). In some section profiles, between 3–5 degenerating labelled cells were ingested by a lectin-labelled AMC (Fig. 21). Occasional mitotic AMC labelled with isolectin were observed (Fig. 22).

DISCUSSION

In agreement with a previous study using silver carbonate staining (LING, 1982), the present results demonstrated a substantial reduction in the population of AMC in the corpus callosum following two or three successive subcutaneous injections of dexamethasone or a single injection of cortisone in postnatal rats. As shown by immunohistochemistry using the monoclonal antibodies OX-42, OX-18, EDI and isolectin staining, less than half of the AMC survived the glucocorticoid treatments. The use of different specific microglial markers now available has therefore greatly strengthened the stance that there is a direct influence of glucocorticoids on the development of amoeboid microglia cells in vivo. Another alteration of the AMC following glucocorticoid injections was the greater diminution of immunoreactivity with advancing age when compared with that of the control rats.

In dexamethasone-injected rats, very few EDI positive cells were observed in the postnatal corpus callosum when compared with the control animals. Since EDI is a monoclonal antibody which recognizes all cells of rat monocyte/macrophages lineage (DUJKSTRA et al., 1985), and since glucocorticoids are known to reduce the number of circulating monocytes leading to a decrease in the number of macrophages (RUSSOMARIE 1992), the decrease in the number of amoeboid microglial cells in the corpus callosum in the present study could be attributed to a decrease in the number of monocytes, which are considered to be their precursor cells (LING et al., 1980, 1982). It is relevant to note that the number of macrophages in the neonatal rat lung was also reduced after dexamethasone administration (LORTIE et al., 1990). Another possible explanation for the reduction in the number of AMC is the acceleration of their spontaneous degeneration known to occur in normal developing corpus callosum (IMAMOTO and LEBLOND, 1978). It was estimated by IMAMOTO and LEBLOND (1978) that two-thirds of the cell population subsequently underwent degeneration over a period of three weeks. It would appear from our results that, through some unknown mechanisms, glucocorticoids might have induced or accelerated the degenerating processes of AMC. The endocytosis of the degenerating AMC by the surviving AMC is probably for facilitating a rapid removal of the dead cells. The essential function of AMC in the postnatal brain is the elimination of cellular debris by phagocytosis, since from late embryonic to early postnatal stages a large number of neurons or oligodendrocytes undergo naturally occurring cell death (CUNNINGHAM, 1982; OPPENHEIM et al., 1990; BARRES et al., 1992). AMC may also be related to neuronal growth through the secretion of neurotrophic factors (NAKAJIMA and KOSHAKA, 1993). A decrease in the number of AMC from the normal may adversely affect the above functions.

Previous studies showed that the round and amoeboid microglial cells in the corpus callosum in normal rats transformed into ramified microglial cells between the 5th and 10th postnatal day (KAUR et al., 1985; KAUR and LING, 1991). Such a process of metamorphic transformation was completed by two weeks of age. In this connection, it is interesting to note that the administration of glucocorticoids in this study appeared to bring about an early differentiation or maturation of amoeboid microglial cells into ramified microglia. Thus, in glucocorticoid-treated rats killed at the age of 7 days, a majority of the OX-42 immunoreactive or lectin-labelled microglial were ramified, while the labelled cells in the control rats of the same age group remained round, morphologically representing a nascent form of the cell type (WU et al., 1992, 1993).

Contrary to the finding by LORTIE et al. (1990), who described that the phagocytic activity of macrophages in the fetal and neonatal rat lungs was reduced following injections of dexamethasone into pregnant and newborn rats, the phagocytic activity of the amoeboid microglial cells which persisted after the glucocorticoid treatments did not appear to be affected, as evidenced by their avid uptake of the
fluorescent dye, RhICl. Accompanying the endocytosis of RhICl, the CR3 receptors on these cells appeared to be vigorously upregulated since most of them appeared round and exhibited intense staining with OX-42, particularly in rats killed at the age of 7 days. The active phagocytic activity of AMC receives further support from their endocytosis of degenerating AMC in our ultrastructural study using lectin labelling. Despite their decrease in number, the proliferative capability of the surviving amoeboid microglial cells does not seem to be affected by the glucocorticoid treatment, as shown by the wide occurrence of bromodeoxyuridine-labelled cells as well as the occurrence of mitotic AMC labelled with lectin. This is consistent with the work by KIEFER and KREUTZBERG (1991), who reported that microglial proliferation was not significantly inhibited by dexamethasone in the facial neucleus following axotomy of the facial nerve. Our results tend to differ from the finding of GANTER et al. (1992) who described a proliferation of microglia in culture as being diminished significantly after the addition of dexamethasone of hydrocortisone.

Previous studies (LING et al., 1990, 1991) showed that the immunoreactivity of microglial cells with OX-42 and OX-18 gradually diminished in the course of their transformation from the round amoeboid form into the ramified type. The strong OX-42 and OX-18 immunoreactivity in the round AMC was related to their active phagocytic activity (LING et al., 1990, 1991). Following glucocorticoid administration in the present study, microglial cells differentiated prematurely into the ramified form, displaying a weak immunoreactivity with OX-42 and OX-18. This suggests a rapid down-regulation of the surface antigens, i.e. CR3 receptors (marked by OX-42) and MHC class I (marked by OX-18) antigen. These receptors may have been shed or masked by ligands as seen in the normal postnatal development (LING et al., 1990, 1991). On the other hand, it would appear that these surface antigens are readily upregulated when the cells are loaded with a foreign substance such as RhICl. This is because the RhICl-labelled cells in dexamethasone-treated rats were more intensely stained with OX-42. Since OX-42 is known to mark CR3 receptors on monocytes and their derivative macrophages (WRIGHT et al., 1983; BELLER et al., 1990), the vigorous expression of CR3 in amoeboid microglia in dexamethasone-treated rats may be related to their active endocytosis of RhICl that had gained access into the nervous tissue. It has been shown earlier by GRAEBER et al. (1988) that activated microglia in the facial nucleus showed an increased expression of CR3 receptors following peripheral nerve injury.

The absence of OX-6 immunoreactivity on amoeboid microglia in both control and glucocorticoid-injected rats indicates the absence of expression of major histocompatibility complex (MHC) class II antigen on these cells, although the surface antigen is readily induced when challenged with the bacterial toxin, lipopolysaccharide (XU and LING, 1994). It seems possible that glucocorticoids may suppress the immunological potentiality of amoeboid microglia in the antigen-presenting function.

Acknowledgements. We thank Mrs. E. S. YONG and Mr. Tajuddin bin M. Ali for their technical assistance, and Ms. D. KAUR for her secretarial help in the preparation of the manuscript.

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