directly to the flank organ, the sebaceous structures increased in size, the effect of 20 and 40 μg DHT solved in acetone being greater than that obtained with the same amount of DHT encapsulated in liposomes (α = 0·05).

Mezei & Gulasekharam (1980, 1982) held that the use of cutaneously applied liposomes would diminish systemic side-effects of encapsulated drugs. This effect, however, can only be partly affirmed by our experiments since although the stimulation of the untreated flank organ after androgen application occurs only after application of DHT in acetone, the drug in liposomes had a smaller effect than that applied in acetone. Yet, in the experiments of Mezei & Gulasekharam (1980, 1982), a four times higher concentration of the tested substance was found when liposomes were used. Several factors might cause the discrepancy between the work of Mezei and Gulasekharam and the present report: (i) different steroids were used; (ii) Mezei & Gulasekharam measured the concentration of the test substance in the skin whereas we measured the biological effect; (iii) different species of animals were used and large differences in percutaneous absorption do occur between different species (Bartek & LaBudde 1975); (iv) the schemes of application were different.

Since our results indicate that a liposome formulation shows a diminished systemic absorption in parallel with a reduced biological effect, we may conclude that DHT when applied in a liposome formulation in our model shows no percutaneous advantages in comparison with more conventional delivery systems.

REFERENCES

Bartek, M. J., La Budde, J. A. (1975) in: Maibach, H. (ed.) Animal Models in Dermatology. Churchill Livingstone, Edinburgh, pp 103–120

Goos, C. M. A. A., Wirtz, P. Vermorken, A. J. M. (1982) Arch. Derm. Res. 273: 333–341

Mezei, M., Gulasekharam, V. (1980) Life Sci. 26: 1473–1477

Mezei, M., Gulasekharam, V. (1982) J. Pharm. Pharmacol. 34: 473–474

Patel, H. M., Ryman, B. E. (1981) in: Knight, C. G. (ed.) Liposomes: from physical structure to therapeutic application. Elsevier/North-Holland Biomedical Press, Amsterdam, pp 409–441

Takayasu, S., Adachi, K. (1972) Endocrinology 90: 73–80

Vermorken, A. J. M., Goos, C. M. A. A., Roelofs, H. M. J. (1980) Br. J. Dermatol. 102: 455–461

Voigt, W., Hsia, S. L. (1973) Endocrinology 92: 1216–1222

J. Pharm. Pharmacol. 1984, 36: 336–337
Communicated November 25, 1983

Effect of L-dopa on glutamate decarboxylase activity in the hypothalamic and amygdaloid nuclei

MASATOSHI ITOH*, AKITO NOHTOMI, NOBUO YUFU, HIDEYUKI UCHIMUA**, *Department of Neuropsychiatry, Faculty of Medicine, Kyushu University, Maidashi 3-1-1, Fukuoka 812 and **Laboratory for Neurochemistry, Hizen National Mental Hospital, Kanzaki, Saga 842-01, Japan*

Repeated administration of L-dopa methylester produced a significant increase in glutamate decarboxylase (GAD) activity without pyridoxal-5'-phosphate in the lateral hypothalamic area and medial amygdaloid nucleus. The effect of L-dopa on GAD activity was opposite to that of haloperidol in the lateral hypothalamic area.

L-Dopa is widely used in the treatment of Parkinson's disease, in which there is a deficiency of GABAergic neurons as well as dopaminergic neurons (Lloyd et al 1976). Moreover, many experiments suggest that a strict functional relationship exists between GABAergic and dopaminergic neurons in mammalian central nervous systems. The interaction between the GABAergic and dopaminergic systems, however, has been studied mainly in the extrapyramidal system. Although the hypothalamic and amygdaloid nuclei contain GABAergic neurons and dopaminergic terminals, limited investigation has been carried out on the possible GABA-dopamine interaction in these areas. In addition, L-dopa treatment has produced a different effect on glutamate decarboxylase (GAD) activity in the regional brain areas (Di Giorgio et al 1979). Therefore, in the present experiment, activity of GAD, an enzyme reponsible for GABA synthesis, was determined in the hypothalamic and amygdaloid nuclei after repeated administrations of L-dopa, and the results were contrasted with those of haloperidol, a dopamine-receptor blocker.

* Correspondence.

Methods

Wistar-King male rats, 250–330 g at the start of the experiment, were housed 4–5 in a cage under standard lighting conditions and maintained with free access to food and water in the home cages. L-Dopa methylester (Sigma) and haloperidol (Dainippon) were dissolved in a 0·9% NaCl (saline) solution just before administration in a volume of 0·5 ml/100 g rat. The animals were either injected intraperitoneally with L-dopa methylester (100 mg kg^{-1}) or with haloperidol (1·5 mg kg^{-1}) twice daily at 8.00 and 20.00 h for 10 consecutive days. The control group was injected with a corresponding amount of saline. The rats were decapitated 60 min after

the last injection. Freeze-dried samples of hypothalamic and amygdaloid nuclei were prepared by the method previously reported (Itoh & Uchimura 1981). GAD activity without pyridoxal-5'-phosphate (PLP) was determined using the radiochemical CO_2-trapping method as described elsewhere (Itoh & Uchimura 1981).

Results and Discussion

As shown in Table 1, repeated administration of L-dopa methylester resulted in a significant increase in GAD activity without PLP in the lateral hypothalamic area and medial amygdaloid nucleus. On the contrary, haloperidol significantly decreased GAD activity without PLP in the lateral hypothalamic area and dorsomedial hypothalamic nucleus.

In previous studies, the effect of L-dopa methylester on GAD activity is less clearly defined. Single administration of L-dopa produced a decrease (Kurtz & Kanfer 1971) or no change in GAD activity (Tunnicliff et al 1976). In the preliminary experiment, GAD activity was not affected in the determined brain nuclei by acute treatment with L-dopa methylester (200 mg kg^{-1}) (data not shown). On the other hand, Di Giorgio et al (1979) reported that chronic treatment with L-dopa induced an elevation of GAD activity in the basal nucleus and brain stem, although no change in GAD activity following chronic treatment with L-dopa was demonstrated by Liu et al (1972) or Tunnicliff et al (1976). In the acute experiments, it has been demonstrated that L-dopa treatment was able to decrease PLP concentration, as a result of the formation of a dopa-PLP Schiff base which may reduce GAD activity (Kurtz & Kanfer 1971; Bayón et al 1977). however, in the present experiment, repeated injections of L-dopa methylester induced an elevation of GAD activity without PLP in the lateral hypothalamic areas and medial amygdaloid nucleus. Therefore, the change in GAD activity in the subacute or chronic studies is not likely to reflect any change in the enzyme activity due to the formation of a dopa-PLP Schiff base (Di Giorgio 1979; Nisticò et al 1980).

In the lateral hypothalamic area, the treatment with L-dopa methylester produced a significant increase in GAD activity without PLP. On the contrary, reduced GAD activity without PLP was found in the lateral hypothalamic area of the haloperidol-treated rats. L-Dopa is a precursor of dopamine and haloperidol is a blocker of the dopamine receptor. Thus, repeated stimulation of dopamine receptors may induce enhancement of GAD activity which reflects GABAergic neuronal activity in the lateral hypothalamic area. In contrast, repeated blockage of dopamine receptors may produce a reduction of GABAergic neuronal function in the lateral hypothalamic area.

Table 1. Effects of repeated administration of L-dopa methylester and haloperidol on GAD activity in hypothalamic and amygdaloid nuclei of the rat.

Nucleus	Control	L-Dopa	Haloperidol
Anterior part of hypothalamus			
Anterior nucleus	2·18 ± 0·05 (5)	2·21 ± 0·17 (5)	1·97 ± 0·12 (5)
Lateral area	1·85 ± 0·06 (6)	2·15 ± 0·10 (5)*	1·52 ± 0·12 (4)*
Medial part of hypothalamus			
Ventromedial nucleus	1·75 ± 0·15 (5)	1·74 ± 0·12 (5)	1·78 ± 0·08 (4)
Dorsomedial nucleus	2·26 ± 0·07 (6)	2·26 ± 0·08 (8)	1·86 ± 0·05 (7)*
Periventricular nucleus	2·22 ± 0·16 (5)	2·40 ± 0·15 (5)	2·13 ± 0·08 (4)
Lateral area	1·73 ± 0·04 (6)	1·85 ± 0·07 (5)	1·45 ± 0·10 (4)*
Arcuate nucleus	0·92 ± 0·07 (5)	0·97 ± 0·07 (5)	0·97 ± 0·10 (4)
Median eminence	0·59 ± 0·06 (5)	0·65 ± 0·07 (5)	0·72 ± 0·10 (4)
Posterior part of hypothalamus			
Posterior nucleus	1·94 ± 0·06 (6)	2·23 ± 0·10 (8)	1·83 ± 0·12 (5)
Lateral area	1·76 ± 0·14 (7)	1·99 ± 0·12 (7)	1·54 ± 0·08 (5)
Amygdala			
Medial nucleus	1·57 ± 0·09 (9)	1·93 ± 0·14 (6)*	1·52 ± 0·12 (6)
Central nucleus	1·21 ± 0·03 (6)	1·25 ± 0·03 (6)	1·09 ± 0·06 (7)
Lateral nucleus	0·80 ± 0·07 (6)	0·91 ± 0·06 (6)	0·73 ± 0·05 (8)
Basal nucleus	0·98 ± 0·08 (4)	1·07 ± 0·07 (6)	0·82 ± 0·11 (5)
Cortical nucleus	1·00 ± 0·08 (6)	1·04 ± 0·05 (7)	1·00 ± 0·08 (5)

L-Dopa methylester (100 mg kg^{-1}) and haloperidol (1·5 mg kg^{-1}) were given twice daily for 10 days. Control animals received saline by the same procedures as the experimental group. The results are expressed as mean values (μmol $^{14}CO_2$ formed g^{-1} dry wt/5 min) ± s.e.m. Number of determination is in parentheses. Significant differences: $*P < 0·05$ (compared with control).

The authors wish to thank Professor Hiroyuki Nakao for his guidance.

REFERENCES

Bayón, A., Possani, L. D., Tapia, M., Tapia, R. (1977) J. Neurochem. 29: 519–525

Di Giorgio, R. M., Macaione, S., Lanotte, M., Nisticó, G. (1979) Neuropharmacology 18: 777–781

Itoh, M., Uchimura, H. (1981) Neurochem. Res. 6: 1277–1283

Kurtz, D. J., Kanfer, J. N. (1971) J. Neurochem. 18: 2235–2236

Liu, Y. P., Ambani, L. M., Vanwoert, M. H. (1972) Ibid. 19: 223–239

Lloyd, K. G., Möhler, H., Bartholini, G., Hornykiewicz, O. (1976) in: Birkmayer, W., Hornykiewicz, O. (eds) Advances in Parkinsonism. Roche, Basle, pp 186–192

Nisticò, G., Ientile, R., Rotiroti, D., Lanotte, M., Di Giorgio, R. M. (1980) J. Pharm. Pharmacol. 32: 663–664

Tunnicliff, G., Butterworth, R. F., Tsukada, Y., Barbeau, A. (1976) Can. J. Physiol. Pharmacol. 54: 79–82