the relative preponderance of noradrenaline (NA) terminals or of NA axons/bodies in each brain area, suggesting that NA metabolism cannot be treated as a single, homogenous system in the CNS; the amygdala region is an example of an area in which terminals predominate, and the midbrain region of an area in which axons/bodies predominate. The effects of oestrogens and amphetamine are shown in Table 1.

NA depletion after synthesis blockade with α-methyl-*p*-tyrosine (500 mg/kg, i.p.) was slower in ovariectomized than in dioestrous litter-mates, including a reduced NA turnover rate; depletion was accelerated by ethinyloestradiol. NA depletion after 4,α-dimethyl-*m*-tyramine (2 × 12.5 mg/kg, i.p.), which reflects changes in NA neuronal uptake mechanisms, was antagonized in the amygdala, but not in the midbrain, regions by ethinyloestradiol.

It is suggested that both amphetamine and oestrogens release newly-synthesized NA, amphetamine by its well-established action of stimulating release from catecholamine terminals, whilst inhibiting impulse flow (Graham & Aghajanian, 1971) and oestrogens by stimulating total turnover of NA. Endogenous ovarian steroids appear to be necessary for the maintenance of 'normal' NA turnover rates; in their absence, or when oestrogen levels are high (at oestrus) so that maximal NA release is already occurring, amphetamine cannot show its expected effects.

References

FLUDDER, J.M. & TONGE, S.R. (1975). Variations in the concentrations of monoamines and their metabolites in eight regions of rat brain during the oestrous cycle: a basis for interactions between hormones and psychotropic drugs. *J. Pharm. Pharmac.*, **27** *Suppl.*, 39.

GRAHAM, A. & AGHAJANIAN, G.K. (1971). Effects of amphetamine on single cell activity in a catecholamine nucleus, the locus coeruleus. *Nature (Lond.)*, **234**, 100–103.

GREENGRASS, P.M. & TONGE, S.R. (1974). Suggestions on the pharmacological actions of ethinyloestradiol and progesterone on the control of monoamine metabolism in three regions from the brains of gonadectomized male and female mice, and the possible clinical significance. *Arch. int. pharmacodyn.*, **211**, 291–303.

L-Dopa and (–)-deprenil in the treatment of Parkinson's disease: a long-term study

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L-Dopa plus a peripheral decarboxylase inhibitor has been used with some success in the treatment of Parkinson's Disease (Birkmayer, Linauer, Mentasti & Riederer, 1974). However, therapeutic success decreases as the illness progresses and various side effects, e.g. on-off effect, occur with this form of treatment.

In a recent study on Parkinsonian patients we demonstrated that deprenil (a selective inhibitor of monoamine oxidase (MAO) 'type B') can significantly potentiate the anti-akinetic effect of L-dopa in akinetic patients (Brikmayer, Riederer, Youdim & Linauer, 1975). Furthermore, the addition of deprenil results in a daily reduction of daily dose requirements of Madopar (L-dopa and the peripheral decarboxylase inhibitor of Benseracide (N-^{1}, DL-seryl-N-^{2}, (2, 3, 4-trihydroxybenzyl) hydrazine)). The aim of this study has been to examine the long-term effects of Madopar plus deprenil treatment in Parkinsonian patients.

Two hundred and twenty-three patients have been treated with Madopar plus deprenil since October 1974. The average oral dose of Madopar was 250 mg three times daily, and of deprenil 5–10 mg once daily. In a few patients 50 mg of L-dopa and 10 mg of deprenil were administered intravenously; in these patients intravenous therapy was more effective than oral therapy but side effects occurred more often and to a greater extent and this mode of treatment was therefore discontinued. As shown in Table 1 the addition of deprenil to Madopar therapy resulted in a statistically significant reduction in patients' functional disability (Birkmayer & Neumayer, 1972). Of the 223 patients, abnormal involuntary movements occurred in 16, psychosis in 14, orthostatic hypotension in 5 and nausea in eight. In patients with side-effects deprenil treatment was either terminated or reduced to 5 mg resulting in the disappearance of some of the side-effects. Madopar-deprenil therapy produced no response in 13.9% of patients.

The improvement in disability following deprenil therapy occurred within 20–120 min after a single dose and lasted for one to three days. Thus, deprenil may act not only by inhibiting MAO but also as a psycho-stimulant by releasing dopamine in a fashion similar to amphetamine (Knoll, Ecseri, Kelemen, Nievel & Knoll, 1965; Fuxe & Ungerstedt, 1970; Christmas, Coulson, Maxwell & Riddell, 1972).

This study has shown that the addition of deprenil

Table 1 Improvement of the disability after Madopar and Madopar plus (–)-deprenil treatment in Parkinsonian patients.

Duration of disease (yrs)	*No.*	*Age (yrs)*	Percentage disability				
			Before therapy		*After Madopar*		*After Madopar + (–)-deprenil*
0–6	115 (55♂, 60♀)	68.5 ± 0.8	54.3 ± 1.5	$P < 0.001$	36.5 ± 1.4	$P < 0.001$	25.3 ± 1.3
7–15	108 (60♂, 48♀)	69.4 ± 0.7	60.1 ± 1.3	$P < 0.001$	37.2 ± 1.4	$P < 0.01$	28.4 ± 1.4

Results are stated as mean ± s.e. mean.

to Madopar therapy results in an improvement of disability independent of the duration of the illness (Table 1) and suggests that the inclusion of deprenil leads to a better utilization of synthesized dopamine from L-dopa.

References

BIRKMAYER, W., LINAUER, W., MENTASTI, M. & RIEDERER, P. (1974). Zweijährige Erfahrungen einer Kombinationsbehandlung des Parkinson-syndroms mit L-dopa und dem Decarboxylasehemmer Benseracide (RO4–4602). *Wien Med. Wochenschr.*, **124**, 340–344.

BIRKMAYER, W. & NEUMAYER, E. (1972). Die moderne medikamentöse Behandlung des Parkinsonismus. *Z. Neurol.*, **202**, 257–280.

BIRKMAYER, W., RIEDERER, P., YOUDIM, M.B.H. & LINAUER, W. (1975). The potentiation of the anti-akinetic effect after L-dopa treatment by an inhibitor of MAO-B, Deprenil. *J. Neurol. Trans.*, **36**, 303–326.

CHRISTMAS, A.J., COULSON, C.J., MAXWELL, D.R. & RIDDELL, D. (1972). A comparison of the pharmacological and biochemical properties of substrate-selective monoamine oxidase inhibitors. *Br. J. Pharmac.*, **45**, 490–503.

FUXE, K. & UNGERSTEDT, U. (1970). Histochemical, biochemical and functional studies on central monoamine neurons after acute or chronic amphetamine administration. In *Amphetamines and Related Compounds*, eds. Costa, L. & Garattini, S., pp. 257–288. New York: Raven Press.

KNOLL, J., ECSERI, Z., KELEMEN, K., NIEVEL, J. & KNOLL, B. (1965). Phenylisopropylmethyl propinylamine (E-250), a new spectrum psychic energizer. *Arch. int. Pharmacodyn.*, **155**, 154–164.

Autoradiographic evidence for the effects of specific uptake-inhibitors on the selective accumulation of [^{3}H]-5-HT by supra-ependymal nerve terminals and for the localization of binding sites for [^{3}H]-D LSD

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It can be shown, by light microscopic autoradiography, that intraventricular injection of tritium-labelled 5-hydroxytryptamine ([^{3}H]-5-HT; 70 μM) leads to its accumulation not only in the brain parenchyma in the rat but also on the ependymal surface of some regions, e.g. corpus callosum, nucleus caudatus and cranial floor of the fourth ventricle; electron microscopy of these regions reveals that the radiolabel is localized to supra-ependymal nerve terminals. The ependymal surface of regions which are known to lack these nerve terminals, e.g. hypothalamus ventralis anterior, eminentia mediana and roof (velum medullare) of the fourth ventricle, was free of label. Intraventricular administration of both [^{3}H]-dopamine (DA; 350 μM) and [^{3}H]-noradrenaline (85 μM) led to their accumulation in the parenchyma but not above the ependyma in all brain regions investigated, i.e. supra-ependymal nerve terminals were not labelled.

Chlorimipramine and reserpine, which block neuronal uptake and storage respectively in