BURN, J. H. (1969). *Ann. Rev. Pharmac.*, **9**, pp. 1–20. Editors: Elliott, H. W., Cutting, W. C. & Dreisbach, R. H. Palo Alto: Annual Reviews, Inc.

HOLLAND, W. C. (1957). *Am. J. Physiol.*, **190**, 492–494.

KHANNA, N. K. & MADAN, B. R. (1968). *Archs int. pharmacodyn. Thér.*, **175**, 136–140.

MADAN, B. R. & KHANNA, N. K. (1970). *Jap. J. Pharmac.*, **20**, 166–167.

MALHOTRA, C. L. & PUNDLIK, P. G. (1965). *Br. J. Pharmac. Chemother.*, **24**, 119–123.

SCHERLAG, B. J., HELFANT, R. H., RICCIUTTI, M. A. & DAMATO, A. N. (1968). *Am. J. Physiol.*, **215**, 1288–1291.

SHARMA, V. N. & PARMAR, N. S. (1967). *Ind. J. med. Res.*, **55**, 60–72.

Effect of apomorphine and pimozide on synthesis and turnover of labelled catecholamines in mouse brain

Labelled tyrosine has been used for the study of catecholamine synthesis and turnover in brain *in vivo* (Udenfriend & Zaltzman-Nirenberg, 1963; Gordon, Reid & others, 1966; Sedvall, Weise & Kopin, 1968; Nybäck & Sedvall, 1970). This method has the advantage that concentrations of endogenous amines in brain are left unchanged. We have now examined the effects of apomorphine and pimozide on accumulation and disappearance of catecholamines formed in mouse brain from [^{14}C]tyrosine.

Apomorphine stimulates dopamine receptors in rat brain (Ernst & Smelik, 1966; Ernst, 1967). Andén, Rubenson & others (1967) and Roos (1969) presented evidence that apomorphine decelerates dopamine turnover in rat brain, possibly by activating a negative feed-back mechanism from the stimulated receptors. In a recent study Persson & Waldeck (1970) obtained results indicating that apomorphine accelerates noradrenaline turnover in mouse brain.

Pimozide is a potent neuroleptic drug (Sterkmans, Brugmans & Gevers, 1968; Haase, Blankenburg-Zahn & others, 1969) and is more effective than chlorpromazine and haloperidol in antagonizing apomorphine-induced stereotyped behaviour (Janssen, Niemegeers & others, 1968). This indicates that the drug is a dopamine receptor blocker. Chlorpromazine and haloperidol accelerate synthesis and turnover of catecholamines in brain (Carlsson & Lindqvist, 1963; Corrodi, Fuxe & Hökfelt, 1967; Nybäck, Borzecki & Sedvall, 1968), effects which probably are due to an activation of the presynaptic neuron as a consequence of the receptor blockade.

After an intravenous injection of [^{14}C]tyrosine to mice, the contents in brain of labelled dopamine and noradrenaline increase during the first 30 min (Nybäck & others, 1968). Between 2 and 7 h after the precursor administration, the labelled amines disappear from brain at rates that appear to be exponential and are not altered by synthesis inhibition with α-methyltyrosine (Nybäck & Sedvall, 1970). Thus, the disappearance of labelled amines during the mentioned time interval will be determined predominantly by the turnover rates of the amines.

Saline or drugs were administered 2 h after the intravenous injection of [^{14}C]tyrosine (10 μCi/animal, 355 mCi/mmol). Groups of animals were killed 2 and 7 h after the precursor administration and the contents in brain of endogenous tyrosine and labelled tyrosine, dopamine and noradrenaline were measured (Nybäck & Sedvall, 1970). In a separate experiment the effect of apomorphine and pimozide on endogenous dopamine and noradrenaline concentrations in brain was measured spectrophotofluorimetrically (Bertler, Carlsson & Rosengren, 1958; Carlsson & Waldeck, 1958).

Apomorphine reduced the content of endogenous noradrenaline to about 70% of controls, whereas pimozide caused a reduction of the dopamine level in mouse brain (Table 1).

Apomorphine retarded whereas pimozide accelerated the rate of disappearance of [^{14}C]dopamine from brain in comparison with saline-treated animals (Table 2).

None of the drugs significantly changed the rate of disappearance of [^{14}C]noradrenaline or the specific activity of [^{14}C]tyrosine.

When [^{14}C]tyrosine was administered by constant rate intravenous infusion for 20 min, the accumulation of labelled dopamine was decreased by apomorphine but increased by pimozide (Table 3). None of the drugs significantly altered the accumulation of [^{14}C]noradrenaline or the specific activity of [^{14}C]tyrosine.

Our results show that turnover of brain dopamine can be accelerated or decelerated by treatment with drugs. The evidence in Table 2 shows that the rate constant for dopamine turnover in brain can be altered more than twice.

Table 1. *Levels of tyrosine and catecholamines in mouse brain 1 h after treatment with saline, apomorphine* (25 mg/kg, i.p.) *or pimozide* (2 mg/kg, orally). Figures represent mean values for groups of five animals ± s.e.

Treatment	Tyrosine μg/g	Dopamine μg/g	Noradrenaline μg/g
Saline	17 ± 1·4	0·59 ± 0·028	0·38 ± 0·014
Apomorphine	16 ± 1·2	0·62 ± 0·039	0·27 ± 0·013†
Pimozide..	18 ± 2·9	0·50 ± 0·026*	0·41 ± 0·027

* Differs from saline group ($P < 0·05$).
† Differs from saline group ($P < 0·001$).

Table 2. *Effect of apomorphine* (25 mg/kg, i.p.) and *pimozide* (2 mg/kg, orally) *on disappearance of catecholamines formed from* [^{14}C]*tyrosine in mouse brain.* Saline or drugs were administered 2 h after the i.v. injection of [^{14}C] tyrosine Animals were killed 2 and 7 h after [^{14}C]tyrosine administration. Rate constants (k) for the disappearance of labelled amines were calculated according to the method of least squares. Figures represent the mean values for groups of 5–7 animals ± s.e.

Treatment	Time h	[^{14}C] Dopamine counts/min g^{-1}	^{k}[^{14}C]-dopamine	[^{14}C] Noradrenaline counts/min g^{-1}	^{k}[^{14}C] Noradrenaline
—	2	2020 ± 160	—	443 ± 46	—
Saline	7	691 ± 39	0·21 ± 0·020	174 ± 11	0·18 ± 0·025
Apomorphine	7	978 ± 38*	0·14 ± 0·019†	157 ± 13	0·20 ± 0·027
—	2	1590 ± 93	—	437 ± 42	—
Saline	7	552 ± 19	0·21 ± 0·013	176 ± 13	0·18 ± 0·024
Pimozide	7	266 ± 30*	0·36 ± 0·026*	184 ± 20	0·18 ± 0·031

* Differs from saline group ($P < 0·001$).
† Differs from saline group ($P < 0·02$).

Tabel 3. *Effect of apomorphine* (25 mg/kg, i.p.) *and pimozide* (2 mg/kg, orally) *on accumulation of catecholamines formed from* [^{14}C]*tyrosine in mouse brain.* [^{14}C]tyrosine was infused i.v. for 20 min starting 40 min after administration of saline or drugs. Immediately after the infusion the animals were killed. Figures represent mean values for groups of 4–6 animals ± s.e.

Treatment	[^{14}C] Dopamine counts/min g^{-1}	[^{14}C] Noradrenaline counts/min g^{-1}
Saline	264 ± 20	111 ± 6
Apomorphine	165 ± 23*	142 ± 18
Saline	348 ± 48	154 ± 16
Pimozide	717 ± 126†	195 ± 12

* Differs from saline group ($P < 0·02$).
† Differs from saline group ($P < 0·01$)

The opposite effects of apomorphine and pimozide on brain dopamine metabolism are of interest with regard to the opposite effects of these drugs on stereotyped behaviour in the rat (Janssen & others, 1968). The selective influence of the two drugs on dopamine synthesis and turnover seems to be more pronounced than that of haloperidol and chlorpromazine since the latter drugs also affect noradrenaline turnover in mouse brain (Carlsson & Lindquist, 1963; Nybäck & others, 1968; Nybäck & Sedvall, 1970).

Persson & Waldeck (1970) found that apomorphine accelerates the disappearance of noradrenaline from mouse brain following synthesis inhibition with α-methyltyrosine. In our experiments apomorphine did not significantly affect synthesis or turnover of [^{14}C]noradrenaline. However, the drug reduced the content of endogenous noradrenaline. Whether apomorphine has a direct or indirect effect on noradrenergic neurons in mouse brain has to be further investigated.

Regarding phenothiazine analogues, we have previously presented evidence that neuroleptic effects are better correlated with changes in dopamine metabolism than with sedative effects that seem to be related to changes in noradrenaline metabolism (Nybäck & others, 1970). The present results support this view, since pimozide, which is a potent neuroleptic drug with negligible sedative properties, markedly accelerated synthesis and turnover of [^{14}C]dopamine but not [^{14}C]noradrenaline.

For generous supply of pimozide, we thank Dr. Oskar Rohte, AB Leo, Hälsingborg.

The present work was supported by the Swedish Delegation for applied medical defence research (project No. 5 : 032/69 and 37 : 032/69) and the Swedish medical research council (project No. B70–40X–2381–03B). The technical assitance of Mrs. Siv Eriksson, Miss Berit Johansson and Miss Heléne Sanderfelt is gratefully acknowledged.

Departments of Pharmacology,
and Psychiatry (s:t Göran's Hospital),
Karolinska Institutet,
S–104 01 *Stockholm* 60,
Sweden.

HENRIK NYBÄCK
JOHAN SCHUBERT
GÖRAN SEDVALL

April 8, 1970

REFERENCES

ANDÉN, N.-E., RUBENSON, A., FUXE, K. & HÖKFELT, T. (1967). *J. Pharm. Pharmac.*, **19**, 627–629.

BERTLER, Å., CARLSSON, A. & ROSENGREN, E. (1958). *Acta physiol. scand.*, **44**, 273–292.

CARLSSON, A. & WALDECK, B. (1958). *Ibid.*, **44**, 293–298.

CARLSSON, A. & LINDQVIST, M. (1963). *Acta pharmac. tox.*, **20**, 140–144.

CORRODI, H., FUXE, K. & HÖKFELT, T. (1967). *Life Sci.*, **6**, 767–774.

ERNST, A. M. (1967). *Psychopharmacologia*, **10**, 316–323.

ERNST, A. M. & SMELIK, P. G. (1966). *Experientia*, **22**, 837–838.

GORDON, R., REID, I. V. O., SJOERDSMA, A. & UDENFRIEND, S. (1966). *Molec. Pharmac.*, **2**, 606–613.

HAASE, H.-J., BLANKENBURG-ZAHN, M., KOESTER, H. & NEUHAUS, B. (1969). *Int. Pharmacopsychiat.*, **3**, 1–12.

JANSSEN, P. A. J., NIEMEGEERS, C. J. E., SCHELLEKENS, K. H. L., DRESSE, A., LENAERTS, F. M., PINCHARD, A., SCHAPER, W. K. A., VAN NUETEN, J. M. & VERBRUGGEN, F. J. (1968). *Arzneimittel-Forsch.*, **18**, 261–287.

NYBÄCK, H. & SEDVALL, G. (1970). *Europ. J. Pharmac.*, **10**, 193–205.

NYBÄCK, H., BORZECKI, Z. & SEDVALL, G. (1968). *Ibid.*, **4**, 395–403.

PERSSON, T. & WALDECK, B. (1970). *Acta physiol scand.*, **78**, 142–144.

ROOS, B.-E. (1969). *J. Pharm. Pharmac.*, **21**, 263–264.

SEDVALL, G., WEISE, V. K. & KOPIN, I. J. (1968). *J. Pharm. exp. Ther.*, **159**, 274–282.

STERKMANS, P., BRUGMANS, J. & GEVERS, F. (1968). *Clin. Trials J.*, **5**, 1107–1112.

UDENFRIEND, S. & ZALTZMAN-NIRENBERG, P. (1963). *Science, N.Y.*, **142**, 394–396.