crease the dopa accumulation following dopa decarboxylase inhibition in both dopamine and noradrenaline neurons indicating that these drugs increase the synthesis of both amines. The effect on the dopamine neurons is probably evoked by stimulation of muscarinic receptors outside the dopamine nerve terminals leading to enhancement of the nerve impulse flow.

This work was supported by the Swedish Medical Research Council (04X-502). H.W. is on leave of absence from Schering AG, Berlin. We are grateful to Maria Lindbäck for skilful technical assistance.

December 20, 1976

REFERENCES

AGHAJANIAN, G. K. & BUNNEY, B. S. (1973). In: *Frontiers in Catecholamine Research*, pp. 643–648, Editors: Usdin, E. & Snyder, S. H. New York: Pergamon.

ANDÉN, N.-E. (1974a). *J. Pharm. Pharmac.*, **26**, 738–740.

ANDÉN, N.-E. (1974b). *Naunyn-Schmiedebergs Arch. Pharmac.*, **283**, 419–424.

ANDÉN, N.-E., MAGNUSSON, T. & STOCK, G. (1974). *Ibid.*, **283**, 409–418.

BARTHOLINI, G. & STADLER, H. (1975). In: *Chemical Tools in Catecholamine Research*, Vol. II, pp. 235–241, Editors: Almgren, O., Carlsson, A. & Engel, J. Amsterdam: North Holland.

CARLSSON, A., DAVIS, J. N., KEHR, W., LINDQVIST, M. & ATACK, C. V. (1972). *Naunyn-Schmiedebergs Arch. Pharmac.*, **275**, 153–168.

CORRODI, H., FUXE, K., HAMMER, W., SJÖQVIST, F. & UNGERSTEDT, U. (1967). *Life Sci.*, **6**, 2557–2566.

JAVOY, F., AGID, Y., BOUVET, D. & GLOWINSKI, J. (1974). *Brain Res.*, **68**, 253–260.

JAVOY, F., AGID, Y. & GLOWINSKI, J. (1975). *J. Pharm. Pharmac.*, **27**, 677–681.

KAŽIĆ, T. (1973). In: *Frontiers in Catecholamine Research*, pp. 897–899, Editors: Usdin, E. & Snyder, S. H. New York: Pergamon.

KEHR, W., CARLSSON, A. & LINDQVIST, M. (1972). *Naunyn-Schmiedebergs Arch. Pharmac.*, **274**, 273–280.

KEHR, W.. CARLSSON, A., LINDQVIST, M., MAGNUSSON, T. & ATACK, C. (1972). *J. Pharm. Pharmac.*, **24**, 744–747.

LAVERTY, R. & SHARMAN, D. F. (1965). *Br. J. Pharmac.*, **24**, 759–772.

MUSCHOLL, E. (1973). In: *Pharmacology and the Future of Man*, vol. 4, pp. 440–457, Editors: Bloom, F. E. & Acheson, G. H. Basel: Karger.

NOSE, T. & TAKEMOTO, H. (1974). *Eur. J. Pharmac.*, **25**, 51–55.

PEREZ-CRUET, J., GESSA, G. L., TAGLIAMONTE, A. & TAGLIAMONTE, P. (1971). *Fedn Proc. Fedn Am. Socs exp. Biol.*, **30**, 216.

ROTH, R. H., WALTERS, J. R. & AGHAJANIAN, G. K. (1973). In: *Frontiers in Catecholamine Research*, pp. 567–574, Editors: Usdin, E. & Snyder, S. H. New York: Pergamon.

SMELIK, P. G. & ERNST, A. M. (1966). *Life Sci.*, **5**, 1485–1488.

VAN ZWIETEN-BOOT, B. J. & PETRI-BOT, A. (1976). *Eur. J. Pharmac.*, **39**, 245–250.

WALTERS, J. R. & ROTH, R. H. (1976). *Naunyn-Schmiedebergs Arch. Pharmac.*, **296**, 5–14.

WESTFALL, T. C. (1974). *Life Sci.*, **14**, 1641–1652.

Modification of electroshock fighting by drugs known to interact with dopaminergic and noradrenergic neurons in normal and brain lesioned rats

M. ANAND*, G. P. GUPTA†, K. P. BHARGAVA†, *Industrial Toxicology Research Centre, Lucknow, and †Department of Pharmacology and Therapeutics, King George's Medical College, Lucknow, India*

The stimulation of certain brain areas—septum, amygdala and lateral hypothalamus, results in marked changes in the electroshock induced fighting behaviour in animals (Anand & Brobeck, 1951; Brady & Nauta, 1953; Woods, 1956; Morgane & Kosman, 1957; Morrison, Barrnett & Mayer, 1958; Ahmad & Harvey, 1968). Changes in the concentration or metabolism of cerebral catecholamines modify the behavioural pattern (Strom-Olsen & Weil Malherbe, 1958; Schild Krant & Kety, 1967; Rubin, 1968). Both adrenaline and dopamine are believed to be involved in the production of aggressiveness (Randrup & Munkvad, 1969; Eichelman, Thoa & Andén, 1972). The present report is concerned with the effect of certain drugs which interact with

* Correspondence.

Table 1. *Effect of certain dopaminergic and noradrenergic drugs on foot electroshock induced fighting in normal rats.* (Each group consisted of 10 animals; all the drugs were given intraperitoneally).

No.	Treatment	Time after treatment (h)	No. of fighting responses (mean ± s.e.) Before drug lesion	After drug lesion	*P*
1	Reserpine (5 mg kg^{-1})	3	11·0 ± 0·45	1·0 ± 0	<·01
2	Apomorphine (1 mg kg^{-1})	0·25	11·8 ± 0·49	20·4 ± 1·12	<·01
3	L-Dopa (150 mg kg^{-1})	2	13·0 ± 0·45	19·0 ± 1·34	<·01
4	Amantadine (100 mg kg^{-1})	2	12·2 ± 0·73	16·4 ± 1·21	<·01
5	Diethyldithiocarbamate (500 mg kg^{-1} daily for 3 days)	1·5	13·0 ± 0·45	27·2 ± 1·02	<·01
6	Imipramine (20 mg kg^{-1})	2	15·8 ± 0·40	9·6 ± 0·51	<·01

dopaminergic and noradrenergic neurons, on the electroshock fighting behaviour in normal and brain lesioned rats.

Adult male albino rats, 200 ± 25 g, had free access to food and water. Fighting was induced in randomly selected pairs of rats by the application of electroshock (2 mA at a frequency of 5 shocks s^{-1}) in the foot in an aggressometer as described by Tedeschi, Tedeschi & others (1959). The fighting episode was considered to have taken place when the animals converged abruptly towards each other and stood face to face on their hind legs and struck or bit at each other. The number of fighting responses during 1 min period of electroshock were counted.

Lesions were made in the septum, or lateral hypothalamus or amygdala by electrolytic coagulation using the stereotaxic instrument for rats (Narighigae Scientific Instrument, Japan) according to Ungerstedt (1971) and the Atlas of DeGroot (1959). The lesioned animals were used for experiments 72 h after the operation. At the end of each experiment, the animals were killed and the site of the lesion was confirmed histologically.

The drugs used were reserpine (Ciba), apomorphine (Mallinkrodt Chem. Works, New York), L-dopa (Brocades), amantadine (Geigy), diethyl dithiocarbamate (BDH) and imipramine (Geigy).

The effects of various drugs on electroshock fighting behaviour in normal and lesioned rats are shown in Tables 1 and 2 respectively. Reserpine significantly reduced the fighting responses in normal and septal lesioned rats. Apomorphine, L-dopa, amantadine and diethyl dithiocarbamate increased the fighting responses while imipramine reduced them in normal animals (Table 1).

The septal lesioned animals showed a significant increase in the fighting responses (Table 2). Treatment with apomorphine also increased the fighting episodes in reserpine treated septal lesioned animals (Table 2). Animals with lesions in the lateral hypothalamus or amygdala showed a marked decrease in fighting episodes which were not changed by reserpine or apomorphine (Table 2).

Reserpine, a depletor of biogenic amines from brain and other tissues (Pletscher, Shore & Brodie, 1955), significantly reduced the electroshock fighting responses in normal rats (Table 1). Apomorphine, a potent agonist of dopaminergic receptors (Andén, Dahlstrom & others, 1966; Ernst & Smelik, 1966) induced a significant increase in electroshock fighting responses. L-Dopa the precursor of dopamine and noradrenaline (Carlsson, 1959) increased the fighting responses (Table 1). Amantadine which increases the synthesis and release of dopamine from the brain (Scatton, Cheramy & others, 1970; Vaatstra & Eigemen, 1974) also increased the fighting responses in normal rats (Table 1). These

Table 2. *Effect of reserpine and apomorphine on electroshock fighting responses in brain-lesioned rats.* Each group consisted of 10 animals. All the drugs were given intraperitoneally.

No.	Drug and dose (mg kg^{-1})	Time after drug (h)	Site of lesion	No. of fighting responses (Mean ± s.e.) Before lesion	After lesion	*P**
1	None		Septum	13·3 ± 1·27	22·2 ± 0·89	< 0·001
2	Reserpine (5)	3	Septum	—	13·0 ± 0·58	N.S.
3	Reserpine (5) + apomorphine (1)	3 0·25	Septum	—	20·2 ± 0·99	< 0·001
1	None	—	Lat. Hypothalamus	12·0 ± 1·10	1·0 ± 0·33	< 0·001
2	Reserpine (5)	3	Lat. Hypothalamus	—	1·0 ± 0·33	< 0·001
3	Reserpine (5) + apomorphine (1)	3 0·25	Lat. Hypothalamus	—	3·0 ± 0·28	< 0·001
1	None	—	Amygdala	12·4 ± 0·33	1·25 ± 0·48	< 0·001
2	Reserpine (5)	3	Amygdala	—	2·25 ± 1·03	< 0·001
3	Reserpine (5) + apomorphine (1)	3 0·25	Amygdala	—	3·25 ± 1·8	< 0·001

* Difference from the responses obtained before lesion.

results suggest a facilitatory effect of dopamine in electroshock fighting behaviour in rats. The fighting responses were markedly increased in animals treated with diethyl dithiocarbamate, a drug which increases the concentration of dopamine and reduced that of noradrenaline (Carlsson, 1959). A significant decrease of fighting responses was observed in animals treated with imipramine (Table 1), which is believed to block the uptake of noradrenaline and increase its concentration at receptor sites (Glowinski & Axelrod, 1964). Thus noradrenaline may be inhibitory for fighting behaviour. Support for the involvement of noradrenaline and dopamine in fighting behaviour is also obtained from our findings that lesion of the septum, an area of the brain particularly rich in noradrenergic neurons (Kaada, 1967) resulted in a significant increase in electroshock fighting responses (Table 2) which were returned to normal by reserpine; further, apomorphine significantly increased the fighting responses in reserpine treated septal lesioned animals (Table 2). The lesion of the lateral hypothalamus induced a significant decrease of fighting responses (Table 2), which were not modified by reserpine or apomorphine treatment. The lesions of the amygdala which is believed to act through the lateral hypothalamus (Magnus & Lammers, 1956; Fernandez de Molina & Hunsperger, 1962) produced a similar effect, that is, a decrease of fighting responses. The results indicate that dopamine has a facilitatory effect and noradrenaline an inhibitory effect in the modulation of electroshock fighting behaviour in rats.

February 21, 1977

REFERENCES

AHMAD, S. S. & HARVEY, J. A. (1968). *J. Comp. physiol. Psychol.*, **66**, 596–602.

ANDÉN, N.-E., DAHLSTROM, A., FUXE, K. & LARSSON, K. (1966). *Acta pharmac. toxic.*, **24**, 263–274.

ANAND, B. K. & BROBECK, J. R. (1951). *Proc. Soc. exp. Biol. Med.*, **77**, 323–324.

BRADY, J. V. & NAUTA, W. J. H. (1953). *J. Comp. physiol. Psychol.*, **46**, 339–346.

CARLSSON, A. (1959). *Pharmac. Rev.*, **11**, 490–494.

DEGROOT, J. (1959). *Verh. K. Med. Akad. Wet.*, **52**, 14.

EICHELMAN, B. S., THOA, N. B. & ANDÉN, N. G. KY. (1972). *Physiol. Behav.*, **8**, 1–3.

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

FERNANDEZ DE MOLINA, A. & HUNSPERGER, R. W. (1962). *J. Physiol., Lond.*, **160**, 200–213.

GLOWINSKI, J. & AXELROD, J. (1964). *Nature*, **204**, 1318–1319.

KAADA, B. R. (1967). In: *Aggression and defense. Neural mechanisms and social patterns.* Editors: Clements, C. D., Lindsley, D. B.; UCLA Forum Med. Sci. 7: 95–133 Los Angeles Univ. California Press.

MAGNUS, O. & LAMMERS, H. J. (1956). *Folia Psychiat. Neurol. Neurochem. Neer.*, **59**, 555–582.

MORGANE, P. J. & KOSMAN, A. J. (1957). *Nature*, **180**, 598–600.

MORRISON, S. D., BARRNETT, R. J. & MAYER, J. (1958). *Am. J. Physiol.*, **193**, 230–234.

PLETSCHER, A., SHORE, P. A. & BRODIE, B. B. (1955). *Science*, **122**, 374–375.

RANDRUP, A. & MUNKVAD, I. (1969). In: *Aggressive behaviour*, p. 228. Editors: Garattini, S. & Sigg, E. B., Amsterdam; Excerpta Medica.

RUBIN, R. T. (1968). *J. psychosom. Res.*, **12**, 171–175.

SCATTON, B., CHERAMY, A., BESSON, M. J. & GLOWINSKI, J. (1970). *Eur. J. Pharmac.*, **13**, 131–133.

SCHILD KRANT, J. J. & KETY, S. S. (1967). *Science*, **156**, 21–30.

STROM-OLSEN, R. & WEIL MALHERBE, H. (1958). *J. Ment. Sci.*, **104**, 696–704.

TEDESCHI, R. E., TEDESCHI, D. H., MUCHA, A., COOK, L., MATTIS, P. & FELLOWS, E. J. (1959). *J. Pharmac. exp. Ther.*, **125**, 28–34.

UNGERSTEDT, U. (1971). *Acta physiol. scand.*, **367**, *Suppl.*, 1–30.

VAATSTRA, W. J. & EIGEMEN, L. (1974). *Eur. J. Pharmac.*, **13**, 131–133.

WOODS, J. W. (1956). *Nature*, **178**, 8698.