Evidence Indicating an Association Between Schizophrenia and Dopaminergic Hyperactivity in the Brain

A. Randrup and I. Munkvad

Introduction

The evidence indicating an association between schizophrenia and brain dopamine is of pharmacological nature. It emerges from studies of two classes of drugs: amphetamines which can produce a schizophrenic-form psychosis and neuroleptics which can antagonize psychotic symptoms in schizophrenic patients.

This paper was presented at the joint meeting of The American Schizophrenia Association, The Canadian Schizophrenia Association and The Schizophrenia Association of Great Britain; London, England, September 28-30, 1871.

Amphetamines, Schizophrenia and Dopamine

There are many reports in the literature about non-psychotic persons developing a temporary psychosis after intake of larger doses of amphetamines (d-amphetamine, methamphetamine, phenmetrazine, etc.). Most authors have observed this in addicts, who have taken amphetamines chronically but cases of psychosis resulting from a single dose or a few doses taken within less than 24 hours are also on record (Griffith et al. 1970; Angrist and Gershon 1971; Be-jerot 1969; older references in Randrup and Munkvard 1967; Kalant 1966).

The symptoms of the "amphetamine psychosis" differ among individuals but in many cases they are very similar to those seen in certain forms of schizophrenia, particularly the paranoid form. The similarity is such that misdiagnoses have frequently been made (Connell 1958; Hampton 1961; Breitner 1963; Mendels 1964; Rickman et al. 1961; Beamish and Kiloh 1960; Bell and Trethowan 1961; Ellinwood 1969; Welsh 1962).

All schizophrenic symptoms have

A. Randrup and I. Munkvad
Sct. Hans Hospital
DK 4000 Roskilde, Denmark

apparently been observed in the amphetamine psychosis including paranoid ideas; auditory hallucinations; autism; abnormal social behavior (aggression, suspiciousness, avoidance of people, etc.), thought blocking and stereotyped behaviour (Sano and Nagasaka 1956; Tatetsu et al. 1956;. Tatet-su 1960; Utena 1966; Kellner 1960; Ellin-wood 1967, 1968 and 1969; Welsh 1962; Griffith et al. 1970; McConnell 1963; Connell 1957 and 1958; Rylander 1969 and 1971; Jonsson and Gunne 1970; Angrist and Gershon 1971; Shanson 1956; Rickman et al. 1961; Silverman 1959; further references in Randrup and Munkvad 1967 and 1970).

Stereotyped behaviour is also seen in animals after larger doses of amphetamines (including apomorphine). This is a very conspicuous and reproducible phenomenon which apparently occurs in all mammals. We have seen it in mice, rats, guinea pigs, rabbits, cats, dogs, squirrel monkeys and vervet monkeys. The kind of activity performed depends on the species. Rodents perform continuous sniffing, licking or biting, cats make continuous head movements as if looking around (stereotyped sniffing or grooming also reported) and monkeys repeat certain movements or simple behavioural patterns continuously (Randrup and Munkvad 1967, 1970 and 1971; Ellin-wood 1969, 1971 and 1971a and in press).

This stereotyped behaviour has been studied extensively in the latest years in various laboratories including our own, and strong evidence now indicates that it is produced by an effect of the amphetamines on dopamine or dopamine receptors in the nigro-striatal system in the brain. This evidence is of biochemical nature (analysis of dopamine and its metabolites as well as other amines in the brain) and of anatomical nature (micro-injections and lesions in the nigro-striatal system), (Randrup and Munkvad 1968, 1970 and 1971a; Jonas and Scheel-Kriiger 1969; Fog and Pakkenberg 1971; Ungerstedt 1971 and 1971a; Unger-stedt et al. 1969; Cools and van Rossum 1970).

In various experiments with rats, mice and monkeys in pairs or groups we found that the stereotyped behaviour was accompanied by social isolation, aggression and other changes in the social behaviour (Schi0rring and Randrup 1971; Kjellberg and Randrup, in press; Hasselager et al. in preparation). The biochemical basis of these social effects has not been extensively studied but recently we found indications that the aggression of amphetamine-treated mice was mediated by dopamine in parallel with the stereotypy (Hasselager et al. in preparation).

Neuroleptics, Schizophrenia and Dopamine

Neuroleptics have therapeutic effects against psychotic symptoms in schizophrenia including stereotyped behaviour, (Munkvad et al., in press) and also antagonize stereotyped behaviour induced by amphetamine or apomorphine in animals. These two effects are highly correlated and testing of the anti-stereotypy effect in rats is used for preclinical evaluation of possible antipsychotic effect of new drugs (Bobonetal. 1970).

The antagonism of stereotyped activity by neuroleptics is not due to a general sedation of the animals. Concurrently with inhibition of the stereotyped, continuous sniffing, licking or biting of rats the neuroleptics cause increase of other activities such as grooming, rearing and locomotion (Randrup and Munkvad 1965; Philips and Bradley 1969; del Rio and Fuentes 1969).

The specific character of the antagonism of amphetamine stereotypies by neuroleptics makes it probable that the neuroleptics inhibit the nigro-striatal dopaminergic system, which is activated by amphetamine (Randrup 1970). This contention is supported by biochemical and anatomical experiments which indicate that neuroleptics of the phenothiazine (e.g. chlorpromazine) or butyrophenone (e.g. haloperidol) types block dopamine receptors, while those of reserpine type disrupt storage mechanisms for dopamine in the neurons (reviews by Munkvad et al. 1968; Bobon et al. 1970; new evidence: Cools and van Rossum 1970; Fog et al. 1971; Scheel-Kniger in press; Nyback et al. 1970; Ungerstedt et al. 1969; Janssen et al. 1968).

Neuroleptic treatment of schizophrenia is often accompanied by neurological side effects (rigidity, tremor, etc.), which are closely reminiscent of Parkinson's disease (Solow 1971 with further references). Since there is strong evidence that Parkinson's disease is due to reduced dopaminergic activity in the nigro-striatal system (Costal et al. 1966; Hornykiewicz, in press) this is another indication of reduction of dopaminergic activity by neuroleptics. In the genuine Parkinson's disease there is therapeutic effect of 1-DOPA which gives rise to increased dopamine in the brain; among the side effects of this therapy are mental symptoms i.a. psychosis, paranoid delusions and stereotyped behaviour (Jenkins and Groh 1970; Barbeau 1970; Knopp et al. 1971; Calne 1970).

It therefore seems that dopamine in the brain is associated with both neurologic and psychotic phenomena. Another example of this is the fact that neuroleptics also have therapeutic effect in various neurologic diseases with symptoms of hyperkinesia e.g. Huntington's chorea (Brand-rup I960; Bruyn 1968; Snyder et al. 1970; Klawan 1970).

Patients with Huntington's chorea often have psychotic symptoms also and may be diagnosed schizophrenics before the hyperkinetic movements start (Panse 1942; Bruyn 1968); this disease was actually studied as a model of schizophrenia by C. and O. Vogt (Kolle 1959).

CONCLUSIONS AND COMMENTS

The evidence which is reviewed (in short fashion) above suggests the hypothesis that in schizophrenic patients (particularly those who benefit best from neuroleptics) there is hyperactivity of the nigro-striatal dopamine system in the brain.

Further test of this hypothesis would be interesting. Particularly there is now a lack of knowledge about the turnover and metabolism of dopamine in the brain of schizophrenics and also about the balance between dopaminergic and other systems in these brains.

In cases of Huntington's chorea the amounts of dopamine and its metabolite homovanilic acid was found within normal limits in the brain and cerebrospinal fluid (Aquilonius and Sjostrom 1971 with further references). An improvement (reduction of involuntary movement) was obtained by therapy with physostigmine which causes an increase of cholinergic activity (Aquilonius and Sjostrom 1971). It is therefore possible that in these choreatic patients there was an excess of dopaminergic relative to cholinergic activity. These results are referred here as an example of the complex problems which may be encountered in studies of brain amines in patients.

REFERENCES

ANGRIST, B. and GERSHON, S.: A pilot study of pathogenic mechanisms in amphetamine psychosis utilizing differential effects of D and L amphetamine. Pharmakopsychiatrie. Neuro-Psychopharmakologie 4, 63-75, 1971.

AQUILONIUS, S.-M. and SJOSTROM, R.: Cholinergic and dopaminergic mechanisms in Huntington's chorea. Life Sci. 10, 405-414, 1971.

BABREAU, A.: Dopamine and disease. C.M.A.J. 103, 824-832, 1970.

BEAMISH, P. and KILOH, L. G.: Psychoses due to amphetamine consumption. J. Ment. Sci. 106, 337-343, 1960.

BEJEROT, N.: Discussion p. 140 in Abuse of Central Stimulants by F. Sjoqvist and M. Tottie. Almqvist & Wiksell, Stockholm 1969.

BELL, D. S. and TRETHOWAN, W. H.: Amphetamine addiction. J. Nerv. Ment. Dis. 133, 489-496, 1961.

BOBON, D., JANSSEN, P. and BOBON, J. (eds.): The Neuroleptics. See i.a. papers by v. Ros-sum et al.; Randrup; v. Rossum; Janssen. S. Karger, Basel 1970.

BRANDRUP, E.: Reserpin og tetrabenacin ved chorea Huntington. Nord. Med. (Danish) 64, 968-969, 1960.

BREITNER, C: Appetite suppressing drugs as an etiologic factor in mental illness. Psychoso-matics 4, 327-333, 1963.

BRUYN, G. W.: Huntington's chorea. Historical, clinical and laboratory synopsis. In Handbook of Clinical Neurology, vol. 6, p. 298-378 by P. J. Vinken and G. W. Bruyn (eds.). North-Holland Publishing Company, Amsterdam 1968.

CALNE, D. B.: 1-Dopa in the treatment of parkinsonism. Clin. Pharmacol. Ther. 11:6, 789-801, 1970.

CONNELL, P. H.: Amphetamine Psychosis. Thesis. Univ. of London, 1957.

CONNELL, P. H.: Amphetamine Psychosis. Mauds-ley Mono. no. 5. Chapman & Hall, Ltd., London, 1958.

COOLS, A. R. and VAN ROSSUM, J. M.: Caudal dopamine and stereotype behaviour of cats. Arch. Int. Pharmacodyn. 187, 163-173, 1970.

COSTA, E., COTE, J. and YAHR, M. D. (eds.): Biochemistry and Pharmacology of the Basal Ganglia. Proceedings of the Second Symposium of Parkinson's Disease. Univ. of Columbia, Raven Press, Hewlett, New York 1966.

ELLINWOOD, E. H., JR.: Amphetamine psychosis:
I. Description of the individuals and process.
J. Nerv. Ment. Dis. 144, 273-283, 1967.

ELLINWOOD, E. H., JR.: Amphetamine psychosis:
II. Theoretical implications. J. Neuropsychiat.
4, 45-54, 1968.

ELLINWOOD, E. H., JR.: Amphetamine psychosis: A multi-dimensional process. Seminars Psy-chiat. 1, 208-225, 1969.

ELLINWOOD, E. H., JR.: "Accidental Conditioning" with chronic methamphetamine intoxication: Implications for a theory of drug habituation. Psychopharmacol. 21, 131-138, 1971.

ELLINWOOD, E. H., JR.: Effect of chronic methamphetamine intoxication in Rhesus monkeys. Biol. Psychiat. 3, 25-32, 1971a.

ELLINWOOD, E. H., JR.: Chronic amphetamine intoxication in several experimental animals. Proceedings of the 7th Congress of the Collegium Internationale Neuro-Psychopharma-cologicum, Prague 1970 edited by O. Vinar. Avicenum Press, Prague (in press).

FOG, R. and PAKKENBERG, H.: Behavioural effects of dopamine and p-hydroxyamphetamine injected into corpus striatum of rats. Exp. Neurol. 31, 75-86, 1971.

FOG, R., RANDRUP, A. and PAKKENBERG, H.: Intra-striatal injection of quaternary butyrophenones and oxypertine: Neuroleptic effect in rats. Psychopharmacol. 19, 224-230, 1971.

GRIFFITH, J. D., CAVANAUGH, H. H., HELD, J. and OATES, J. A.: Experimental psychosis induced by the administration of d-amphetamine. Symposium on Amphetamines and Related Compounds, pp. 897-904 edited by E. Costa and S. Garattini. Raven Press, New York, 1970.

HAMPTON, W. H.: Observed psychiatric reactions following use of amphetamine-like substances. Bull. NY Acad. Med. 37, 167-175, 1961.

HASSELAGER, E., ROLINSKI, Z. and RANDRUP, A.: Specific antagonism by dopamine inhibitors of items of aggressive behaviour induced in mice by amphetamine (in preparation).

HORNYKIEWICZ, O. (Ed.): The Pharmacology of the Extrapyramidal System. Section 25 of the International Encyclopedia of Pharmacology and Therapeutics (Eds. Bovet, D. et al.). Per-gamon (in press).

JANSSEN, P., NIEMEGEERS, C, SCHELLEKENS, K., DRESSE, A., LENAERTS, F., PINCHARD, A., SCHAPER, W., VAN NUETEN, J. and VERBRUG-GEN, F.: Pimozide, a chemically novel, highly potent and orally long-acting neuroleptic drug. Arzneim.-Forsch. (Drug Research) 18, 261-287, 1968.

JENKINS, R. B. and GROH, R. H.: Mental symptoms in Parkinsonian patients treated with 1-dopa. Lancet, II, 177, 1970.

JONAS, W. and SCHEEL-KRUCER, J.: Amphetamine induced stereotyped behaviour correlated with the accumulation of O-methylated dopamine. Arch. Int. Pharmacodyn. 177, 379-389, 1969.

JONSSON, L.-E. and GUNNE, L.-M.: Clinical studies of amphetamine psychosis. Symposium on Amphetamines and Related Compounds, pp. 929-936, edited by E. Costa and S. Garattini. Raven Press, New York 1970.

KELLNER, E.: Preludinsucht und Preludinpsychose. Ther. Gegenw. 11, 524-530, 1960.

KJELLBERG, B. and RANDRUP, A.: The effects of amphetamine and pimozide, a neuroleptic, on the social behaviour of vervet monkeys (Cer-copithecus sp.). Proceedings of the 7th Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Prague 1970 edited by O. Vinar. Avicenum Press, Prague (in press).

KLAWAN, H. L.: A pharmacologic analysis of Huntington's chorea. Europ. Neurol. 4, 148, 1970.

KNOPP, W.: Pharmacopsychiatry, 1-dopa and Parkinson's disease. Proceedings of the 7th Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Prague 1970 edited by O. Vinar. Avicenum Press, Prague (in press).

KOLLE, K.: Grosse Nervenarzte, Vol. 2. Georg Thieme Verlag, Stuttgart 1959.

MCCONNELL, W. B.: Amphetamine substances in mental illnesses in Northern Ireland. Brit. J. Psychiat. 109, 218-224, 1963.

MENDELS, J.: Paranoid psychosis associated with phenmetrazine addiction. Brit. J. Psychiat. 110, 865 only, 1964. MUNKVAD, I., PAKKENBERG, H. and RANDRUP, A.: Aminergic systems in basal ganglia associated with stereotyped hyperactive behaviour and cataleptsy. Brain, Behav., Evol. (S. Karger, Basel) 1, 89-100, 1968.

MUNKVAD, I., HEIN, G. and HERSKIN, B.: Treatment of chronic schizophrenic patients with pimozide. Proceedings of the 7th Congress of the Collegium Internationale Neuro-Psycho-pharmacologicum, Prague 1970 edited by O. Vinar. Avicenum Press, Prague (in press).

NYBACK, H., SCHUBERT, J. and SEDVALL, G.: Effect of apomorphine on synthesis and turnover of labelled catecholamines in mouse brain. J. Pharm. Pharmacol. 22, 622-624, 1970.

PANSE, F.: Die Erbchorea. G. Thieme Verlag, Leipzig, pp. 5-122, 1942.

PHILLIPS, M. I. and BRADLEY, P. B.: The effct of chlorpromazine and d-amphetamine mixtures on spontaneous behaviour. Int. J. Neurophar-macol. 8, 169-176, 1969.

RANDRUP, A. and MUNKVAD, I.: Special antagonism of amphetamine-induced abnormal behaviour. Psychopharmacol. 7, 416-422, 1965.

RANDRUP, A. and MUNKVAD, I.: Stereotyped activities produced by amphetamine in several animal species and man. Psychopharmacol. 11, 300-310, 1967.

RANDRUP, A. and MUNKVAD, I.: Behavioural stereotypies induced by pharmacological agents. Pharmakopsychiat. Neuro-Psychopharmakol. (G. Thieme, Stuttgart) 1, 18-26, 1968.

RANDRUP, A. and MUNKVAD, I.: Biochemical, anatomical and psychological investigations of stereotyped behaviour induced by amphetamines. Symposium on Amphetamines and Related Compounds, pp. 695-713 edited by E. Costa and S. Garattini. Raven Press, New York, 1970.

RANDRUP, A. and MUNKVAD, I.: Behavioural toxicity of amphetamines studied in animal experiments. In: The Correlation of Adverse Effects in Man with Observations in Animals edited by S. B. de Baker, pp. 6-17, Excerpta Medica. Int. Cong. Ser. no. 220, Amsterdam, 1971.

RANDRUP, A. and MUNKVAD, I.: Correlation between specific effects of amphetamines on the brain and on behavior. Symposium on Current Concepts on Amphetamine Abuse, Duke University 1970 edited by E. H. Ellinwood, Jr. (in press).

RICKMAN, E. E., WILLIAMS, E. Y. and BROWN, R. K.: Acute toxic psychiatric reactions related to amphetamine medication. Med. Ann. DC 30, 209-212, 1961.

Rio DEL, J. and FUENTES, J. A.: Further studies on the antagonism of stereotyped behaviour induced by amphetamine. Europ. J. Pharmacol. 8, 73-78, 1969.

RYLANDER, G.: Clinical and medico-criminological aspects of addiction to central stimulating drugs. In: Abuse of Central Stimulants, p. 251 edited by F. Sjoqvist and M. Tottie. Almqvist and Wiksell, Stockholm, 1969.

RYLANDER, G.: Stereotype behaviour in man following amphetamine abuse. In: The Correlation of Adverse Effects in Man with Observations in Animals edited by S. B. de Baker, pp. 28-31, Excerpta Medica Int. Congr. Ser. no. 220, Amsterdam, 1971.

SANO, I. and NAGASAKA: Uber chronische Weck-aminsucht in Japan. Fortschr. Neuro. Psychiat. 24, 391-394, 1956.

SCHEEL-KRUGER, J.: Comparative studies of various amphetamine analogues demonstrating different interactions with the metabolism of the catecholamines in the brain. Europ. J. Pharmacol. 14, 47-59, 1971.

SCHEEL-KRUGER, J.: Studies on the accumulation of 0-methylated dopamine and noradrenaline in the rat brain following various neuroleptics, thymoleptics and aceperone. Arch. Int. Phar-macodyn (in press).

SCHI0RRING, E. and RANDRUP, A.: Social isolation and changes in the formation of groups induced by amphetamine in an open field test with rats. Pharmakopsychiatrie Neuro-Psycho-pharmakologie 4, 2-11, 1971.

SHANSON, B.:Amphetamine poisoning. Brit. Med. J., March 10, 576 only, 1956.

SILVERMAN, M.: Subacute delirious state due to "Preludin" addiction. Brit. Med. J., March 14, 696-697, 1959.

SNYDER, S., TAYLOR, K., COYLE, J. and MEYER-HOFF, J.: The role of brain dopamine in behavioral regulation and the actions of psychotropic drugs. Amer. J. Psychiat. 127, 117-125, 1970.

SOLOW, C: Drug therapy of mental illness: tranquilizers and other depressant drugs. In: An Introduction to Psychopharmacology edited by R. H. Rech and K. E. Moore, pp. 289-319, Raven Press 1971.

TATETSU, S., GOTO, A. and FUTIWARA, T.: The methamphetamine-psychosis (Kakuseizai chu-dolsa). Igaku Shoin, Tokyo 1956. Nat. Libr. Med. Cat. 1955-59.

TATETSU, S.: Pervitin-Psychosen. Folia Psychiat. Neurol. Jap. Suppl. 6, 25-33, 1960.

UNGERSTEDT, U., BUTCHER, L., BUTCHER, S., ANDEN, N.-E. and FUXE, K.: Direct chemical stimulation of dopaminergic mechanisms in the neostriatum of the rat. Brain Res. 14, 461-471, 1969.

UNGERSTEDT, U.: Striatal dopamine release after amphetamine or nerve degeneration revealed by rotational behaviour. Acta Physiol. Scand. Suppl. 367, 49-68, 1971.

UNGERSTEDT, U.: Postsynaptic supersensitivity after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system. Acta Physiol. Scand. Suppl. 367, 69-93, 1971a.

UTENA, H.: Behavioural aberrations in metham-phetamine-intoxicated animals and chemical corelates in the brain. In: Correlative Neuro-sciences, vol. 21B, pp. 191-207 edited by T. Tokizane and J. P. Schade. Elsevier, Amsterdam, 1966.

WELSH, A. L.: Side effects of anti-obesity drugs. Charles C. Thomas, Springfield, 111., U.S.A. 1961.

Editorial Comments . . .

Continued from inside front cover

'The literature of the last twenty-five years is a bewilderment rather than a guide to the practical clinician. This implies no disparagement of greatly improved experimental methods of drug testing, of double-blind techniques and statistical sophistication generally: but one can not get out of a series of observations, however treated mathematically, more data than was actually observed and recorded. The attentive and discriminating observer who adds daily to his experience over a period of years, has the possibility of insights that can be gained in no other way and are certainly beyond the reach of experimental design—.'

In the Journal of ORTHOMOLECULAR PSYCHIATRY, "The attentive and discriminating observer" will have a voice in unison with those who are statistically sophisticated.

J. Ross MACLEAN, M.D.