Life Sciences, Vol. 44, pp. 1521-1525 Pergamon Press
Printed in the U.S.A.

MINIREVIEW

NICOTINE AND CANNABINOIDS AS ADJUNCTS TO NEUROLEPTICS IN THE TREATMENT OF TOURETTE SYNDROME AND OTHER MOTOR DISORDERS

D.E. Moss, Patricia Z. Manderscheid*, S.P. Montgomery, Andrew B. Norman*, and Paul R. Sanberg*

Laboratory of Psychobiochemistry, University of Texas at El Paso, El Paso, Texas 79968 and *Laboratory of Behavioral Neuroscience, Department of Psychiatry, University of Cincinnati School of Medicine, Cincinnati, Ohio 45267

Summary

Animal studies suggest nicotine and cannabinoids may significantly enhance the therapeutic value of neuroleptics in motor disorders. This was recently demonstrated in humans by the finding that chewing nicotine gum produced striking relief from tics and other symptoms of Tourette syndrome not controlled by neuroleptic treatment alone. It appears that the use of nicotine or cannabinoids may greatly improve the clinical response to neuroleptics in motor disorders.

The use of nicotine and cannabinoids to treat extrapyramidal motor disorders has a long history. For example, applications of nicotine in motor disorders have been suggested by the report that it relieves hemidystonia (1). There are also numerous reports of the use of marijuana to treat a wide variety of neurological disorders involving the basal ganglia during the 19th and early 20th centuries (2). More recently it has been reported that marijuana produces therapeutic effects equal to diazepam in torsion dystonia (3), cannabidiol can relieve dystonic movement disorders (4) and symptoms of chorea in Huntington's disease (5). The purpose of this paper is to review the use of nicotine or cannabinoids concurrently with neuroleptics.

Animal Research

New interest in cannabinoids in the treatment of motor disorders is the result of the recent discovery that delta-9-tetrahydrocannabinol (THC), cannabidiol, and levonantradol (LEVO, a synthetic cannabinoid) strongly potentiate (up to 100 fold) neuroleptic-induced hypokinesia (6,7,8). Nicotine has also received additional attention as a possible therapeutic agent because of the hypothesis that the cannabinoids produce their powerful effects on the extrapyramidal motor system through a nicotinic cholinergic mechanism (8,9).

0024-3205/89 $3.00 + .00

In these experiments, hypokinesia induced by neuroleptics, cannabinoids, and nicotine were measured by the bar test wherein rats were placed with their front paws on a bar 9 cm above the base (6). The time required for them to remove themselves from a standing position at the bar was a simple measure of hypokinesia. In this test, nicotine and cannabinoids alone produce either no hypokinesia (THC and nicotine) or only a slight effect (LEVO). These compounds, however, produce powerful increases in reserpine- and fluphenazine-induced hypokinesia (Figures 1 and 2). Similar effects are obtained after haloperidol is combined with THC (7) or nicotine (10). It should be noted that the effect of LEVO is severely underestimated in Figure 1 insofar as all rats in this group actually remained at the bar more than 1 hr and one longer than 2 hr.

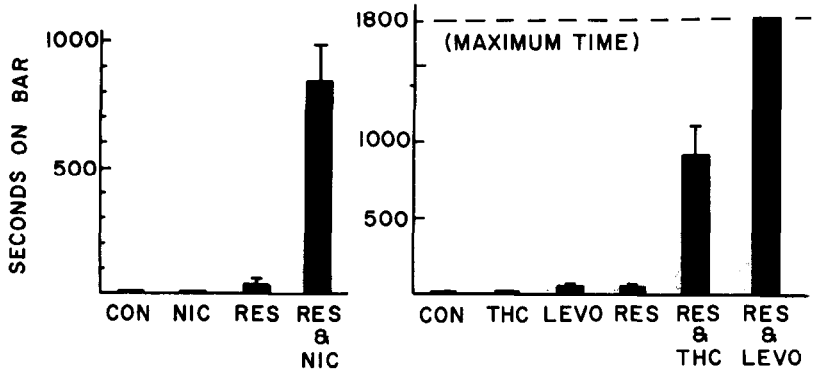

Figure 1. Hypokinesia in rats pretreated with vehicle (CON) or reserpine (RES, 7.5 mg/kg IP 18 to 24 hr before tests), with or without a second administration of nicotine (NIC, 1.0 mg/kg IP 1 hr before test), THC or LEVO (both 10 mg/kg by gavage 4 hr before test). The arbitrary maximum time allowed for a bar test was 30 min (1800 sec). Note the difference in the scale in the two panels. [redrawn from Montgomery et al. (8) with permission]

The effect of nicotine shown in Figures 1 and 2 has been confirmed in an additional study using haloperidol pretreatment (11). In this rat study, as in those described above, nicotine alone produced no hypokinesia but it produced a very large potentiation of haloperidol-induced hypokinesia. Taken together, all of the experiments show that nicotine and cannabinoids produce similar potention of hypokinesia induced by the dopamine antagonists haloperidol, fluphenazine, and reserpine.

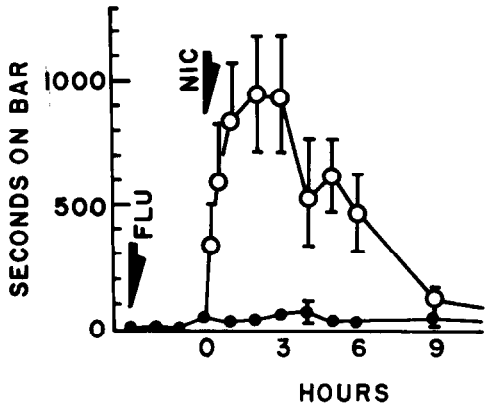

Figure 2. Time course of hypokinetic behavior of rats pretreated with fluphenazine alone (FLU, 0.1 mg/kg IP, filled circles) or FLU followed by an injection of NIC (0.1 mg/kg IP, open circles).

The extreme response to cannabinoids and nicotine in animals pretreated with dopamine antagonists led to the hypothesis that nicotine and cannabinoids may act through a common neurophysiological mechanism in the extrapyramidal system. Furthermore, that the mechanism was probably nicotinic cholinergic in nature (8). This hypothesis has received some support. The involvement of the extrapyramidal system is indicated by the finding that local intracranial injections of nicotine or LEVO directly into extrapyramidal areas produce the entire hypokinetic effect (8). Secondly, a high affinity stereoselective pharmacologically distinct cannabinoid receptor has been discovered (12) to show a high level of binding in the globus pallidus and substantia nigra (13). Lastly, that cannabinoids and nicotine may both act through a nicotinic cholinergic mechanism is supported by the finding that the effects of either can be blocked by mecamylamine, a CNS active nicotinic antagonist (9).

Recent Developments in Clinical Research

The powerful potentiation of neuroleptic effects by cannabinoids and nicotine in animals led to the obvious hypothesis that these compounds might increase the efficacy of neuroleptics in hyperkinetic motor disorders when neuroleptics alone produce marginal but incomplete clinical improvement. In response to this hypothesis, nicotine chewing gum was recently tested as an adjunct in the treatment of difficult cases of Tourette's syndrome which were refractory to haloperidol alone.

In the first limited clinical test, it was reported that chewing nicotine gum, when added to continuing haloperidol treatment, produced rapid, striking, and marked relief from tics and other symptoms of Tourette syndrome not controlled by haloperidol alone (14). Chewing regular gum did not affect the disorder. Therefore, improvement could not at attributed to the chewing act which has been reported to produce improvement in facial tics in mild cases of Tourette's syndrome (15).

In a more complete study of the effects of nicotine in ten additional cases of Tourette syndrome (nine males, one female, mean age 12), nicotine gum produced significant decreases in tic severity and improvement in attention span and concentration in eight subjects (11). The improvement in attention, concentration, and amelioration of hyperactivity and tics allowed the children to do homework and other quiet tasks which they could not do previously (11).

Although these clinical studies involved a very small sample and additional research will be required, these are the first clear clinical demonstrations that nicotine or cannabinoids might potentiate the clinical efficacy of dopamine antagonists in the treatment of motor disorders (6,8,9). It was encouraging to note the improvement in attention and concentration (11) although it is not clear how much such improvement was due to simply controlling the motor symptoms. In any case, however, these results provide important clinical support for the hypothesis that Tourette's syndrome and other hyperkinetic movement disorders may be "acetylcholine deficiency" as well as "dopamine excess" syndromes (16,17). Furthermore, the acetylcholine deficiency may be nicotinic in character. Further research into this relatively understudied possibility will be required in order to exploit the maximum therapeutic potential.

Summary

The value of the present research is the demonstration that nicotine and cannabinoids should add significantly to the well known therapeutic effects of neuroleptics in motor disorders. The use of nicotine or cannabinoids as adjuncts to neuroleptics may improve the clinical response as well as reduce the risk of side effects (e.g., tardive dyskinesia and sedation) by reducing the dose of neuroleptic required. In this regard, it is also significant to note that LEVO antagonizes the compensatory acceleration of striatal dopamine synthesis induced by haloperidol (18). Further research will, however, be required to assess the effects of adjunctive therapy with nicotine or cannabinoids on changes in receptor binding and other basic neuropharmacological mechanisms. In conclusion, the use of nicotine or cannabinoids as adjuncts to neuroleptics may provide significant new opportunities to improve the treatment of a variety of dystonias and hyperkinetic motor disorders.

Acknowledgments

Supported in part by NIMH (RR 08012) and NIDA. Levonantradol and fluphenazine HCL were generous gifts from Pfizer Pharmaceuticals (Groton, Conn.) and E.R. Squibb and Sons (Princeton, N.J.), respectively.

References

1. A.J. LEES Lancet 2 871 (1984)
2. P. CONSROE and S.R. SNIDER (1986) In: Cannabinoids as Therapeutic Agents (Mechoulam R., Ed.), 22-49, CRC Press, Boca Raton (1986).

3. C.D. MARSDEN In: Disorders of Movement, Current Status of Modern Therapy (Barbeau A., Ed.), Vol. 8, 81-104, Lippincott, Philadelphia (1981).
4. P. CONSROE, R. SANDYK and S.R. SNIDER Intern. J. Neurosci. 30 277-282 (1986)
5. R. SANDYK, P. CONSROE, L. STERN, S.R. SNIDER, and D. BLIKLEN In: Marijuana: An International Research Report, (Chesher G., Consroe P., and Musty R., Eds.), 157-162, Monograph Series No. 7, Australian Government Publishing Service, Canberra, Australia (1988).
6. D.E. MOSS, S.B. MCMASTER and J. ROGERS Pharmacol. Biochem. Behav. 15 779-783 (1981)
7. D.E. MOSS, S.P. MONTGOMERY, A.A. SALO and R.W. STEGER In: The Cannabinoids: Chemical, Pharmacologic, and Therapeutic Aspects (Agurell S., Dewey W.L., and Willette R.E., Eds.), 815-828, Academic Press, New York (1984).
8. S.P. MONTGOMERY, D.E. MOSS and P.Z. MANDERSCHEID In: Marihuana '84 (Harvey D.J., Paton W., and Nahas G.G., Eds.), 295-302, IRL Press Limited, Oxford, England (1985).
9. D.E. MOSS, P.Z. MANDERSCHEID, H. KOBAYASHI and S.P. MONTGOMERY In: Marijuana: An International Research Report, (Chesher G., Consroe P., and Musty R., Eds.), 359-364, Monograph Series No. 7, Australian Government Publishing Service, Canberra, Australia (1988).
10. P.Z. MANDERSCHEID, P.R. SANBERG, A.B. NORMAN, H.M. FOGELSON, B.J. MCCONVILLE and D.E. MOSS Soc. Neurosci. Abstr. 14 1257, (1988).
11. P.R. SANBERG, B.J. MCCONVILLE, H.M. FOGELSON, P.Z. MANDERSCHEID, K.W. PARKER, M.M. BLYTHE, W.M. KLYKYLO, and A.B. NORMAN Biomed. Pharmacothera. 42 (in press)
12. W.A. DEVANE, F.A. DYSARZ, M.R. JOHNSON, L.S. MELVIN, and L.S. HOWLETT Mol. Pharmacol. 34 605-613 (1988)
13. M. HERKENHAM, M.D. LITTLE, M.R. JOHNSON, L.S. MELVIN, A.C. HOWLETT, R.B. ROTHMAN, B. DECOSTA, and K.C. RICE Soc. Neurosci. Abst. 14 104 (1988)
14. P.R. SANBERG, H.M. FOGELSON, P.Z. MANDERSCHEID, K.W. PARKER, A.B. NORMAN and B.J. MCCONVILLE Lancet 1 592 (1988)
15. C.B. BRILL Pedia. Neurol. 4 128 (1988)
16. S.M. STAHL and P.A. BERGER In: Gilles de la Tourette Syndrome, (A.J. Friedhoff and T.N. Chase, Eds.). Raven Press, New York, 141-150 (1982).
17. G.S. ROSENBERG and K.L. DAVIS In: Gilles de la Tourette Syndrome, (A.J. Friedhoff and T.N. Chase, Eds.). Raven Press, New York, 407-412 (1982).
18. B.K. KOE Eur. J. Pharmacol. 70 231-236 (1981)