EVANS, B., IWAYAMA, T. & BURNSTOCK, G. (1973). *J. Pharmac. exp. Ther.*, **185**, 60–69.
FLEMING, W. W. (1971). *Ibid.*, **176**, 160–166.
GANNON, B. J., IWAYAMA, T., BURNSTOCK, G., GERKENS, J. & MASHFORD, M. L. (1971). *Med. J. Aust.*, **2**, 207–208.
JANDHYALA, B. S., CLARKE, D. E. & BUCKLEY, J. P. (1974). *J. pharm. Sci.*, **63**, 1497–1513.
JENSEN-HOLM, J. & JUUL, P. (1971). *Acta pharmac. tox.*, **30**, 308–320.
JOHNSON, E. M., Jr., MACIA, R. A. & YELLIN, T. O. (1977). *Life Sci.*, **20**, 107–112.
JUUL, P. & MCIASSAC, R. L. (1973). *Acta pharmac. tox.*, **32**, 382–389.
LAVERTY, R. (1973). *Br. Med. Bull.*, **29**, 152–157.
Physicians' Desk Reference to Pharmaceutical Specialities and Biologicals (1973). 27th edn, p 668. Oradell, New Jersey: Medical Economics, Inc.
SANNERSTEDT, R. & CONWAY, J. (1970). *Am. Heart J.*, **79**, 122–127.
STOCKS, A. E. & ROBERTSON, A. (1967). *Ibid.*, **73**, 569–570.
TRENDELENBURG, U. (1963). *Pharmac. Rev.*, **15**, 225–276.
VILLARREAL, H., EXAIRE, J. E., RUBIO, V. & DAVILA, H. (1964). *Am. J. Cardiol.*, **14**, 633–640.

5-Methoxy-*NN*-dimethyltryptamine: differential modulation of the rewarding and aversive components of lateral hypothalamic self-stimulation

J. D. SINDEN*, D. M. ATRENS, *Department of Psychology, University of Sydney, Sydney N.S.W. 2006, Australia*

It is well established that the catecholamines noradrenaline and dopamine exert a significant excitatory role in self-stimulation behaviour (German & Bowden, 1974). At the same time, 5-hydroxytryptamine (5-HT) has traditionally been seen as having a complementary inhibitory role. The inhibitory role of 5-HT is supported by the widely cited report that *p*-chlorophenylalanine (*p*CPA), a 5-HT synthesis inhibitor, increased the rate of medial forebrain bundle self-stimulation (Poschel & Ninteman, 1971). However, in contrast to the facilitation reported by Poschel & Ninteman (1971) there are also data showing that *p*CPA has no effect on medial forebrain bundle self-stimulation and that it produces an inhibitory effect on raphé or caudate-putamen self-stimulation (Miliaressis, Bouchard & Jacobowitz, 1975; Phillips, Carter & Fibiger, 1976). Interpretation of such widely divergent results is complicated by a number of factors, not the least of which is the complex sequence of monoamine depletion produced by *p*CPA. To further explicate the role of 5-HT in self-stimulation it would seem advisable to explore the effects of drugs that have a more selective effect on 5-HT availability.

Recent studies have shown that the selective 5-HT reuptake blockers LU 10-171 (1-[3-(dimethylamino) propyl]-1-(*p*-fluorophenyl)-5-phthalancarbonitrile) and fluoxetine have an inhibitory effect on lateral hypothalamic self-stimulation (Atrens, Ungerstedt & Ljungberg, 1977; Katz & Carroll, 1977). Atrens & others (1977) showed that this effect was specific to the rewarding component of intracranial stimulation (ICS) and could be clearly dissociated from any non-specific behavioural inhibition. In addition they showed that the specific blockade of noradrenaline reuptake with LU 5-003 produced a similar reduction in self-stimulation reward. They suggested that any pharmacological agent that increased availability of noradrenaline or 5-HT in a response independent manner should attenuate self-stimulation. Using an entirely different paradigm, Franklin & Herberg (1977) arrived at a similar conclusion.

In the present experiment the effects on self-stimulation of 5-methoxy-*NN*-dimethyltryptamine (5-MeODMT), a hallucinogenic indolealkylamine believed to be an agonist at both pre- and postsynaptic 5-HT receptors (Aghajanian & Haigler, 1975) were studied. The use of a two-way shuttle box permitted the differentiation of specific reward and aversion modulation effects from non-specific performance changes.

Eight male Wistar rats, 250–300 g, received stereotaxic implants on 254 μm monopolar stainless-steel electrodes insulated except for the flat cross-section at the tips. The reference electrode was attached to a screw on the skull. Lateral hypothalamic co-ordinates relative to bregma with the skull in a flat position were 2·5 mm posterior, 1·7 mm lateral and 8·7 mm ventral. After postoperative recovery, the rats were tested for self-stimulation in a shuttle box apparatus described previously (Atrens & Becker, 1975; Hunt, Atrens, & others, 1976; Atrens & others, 1977). The ICS consisted of 50 Hz biphasic square wave pulses of 200 μs duration with an anodal pulse immediately following each cathodal pulse. Electronic programming and recording equipment recorded the latencies to initiate and escape ICS which are respectively indices of

* Correspondence.

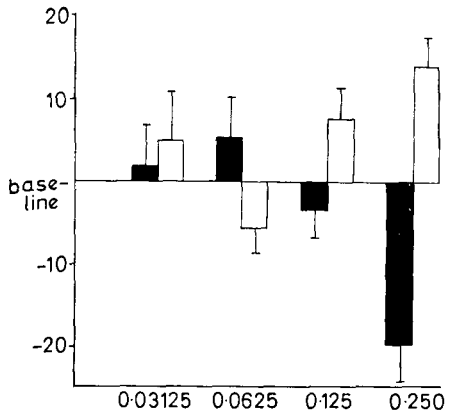

FIG. 1. The effects of four doses of the indolealkylamine 5-methoxy-*NN*-dimethyltryptamine (mg kg^{-1}, abscissa) on shuttle-box self-stimulation. The data are presented as mean percentage changes with the T-bar indicating one standard deviation. Both latency to initiate ICS (closed columns) and latency to escape ICS (open columns) at the 0·250 mg kg^{-1} doses are significantly different from baseline ($P < 0.05$, Willcoxon test). Ordinate: mean percent change in response latencies.

the rewarding and aversive components of ICS (Atrens & Becker, 1975).

A daily session consisted of 5 min of warm-up followed by 10 min of data collection for each rat. Rats were run daily until both response latencies had fully stabilized. The drug was administered on the same day each week with the previous day's run acting as baseline. The drug was not administered unless the baseline had restabilized from the previous week. 5-Methoxy-*NN*-dimethyltryptamine (Sigma) was mixed with tartaric acid, adjusted to pH 5 and administered intraperitoneally in a random order of 4 doses (0·03125, 0·0625, 0·125 and 0·25 mg kg^{-1}) immediately before the warm-up period preceding testing.

Preliminary observations had revealed that 5-MeODMT at doses of 0·50 mg kg^{-1} and above produced marked ataxia, tremor and stereotyped sniffing similar to the 'serotonergic syndrome' described by Trulson & Jacobs (1976). Since these responses were obviously grossly incompatible with the performance of any self-stimulation response, the present study employed 0·25 mg kg^{-1} as the highest dose.

At the conclusion of the experiment, the animals were killed with an overdose of anaesthetic. The brains were rapidly dissected then frozen and sectioned in an American Optical cryostat. The 40 μm sections were mounted and stained with toluidine blue-O. Electrode locations were made with reference to the atlas of Konig & Klippel (1963).

Histological examination revealed that all electrodes were located in the lateral hypothalamus. As there was no indication of differential drug effects due to electrode location, the data have been pooled for all electrode sites.

The data in Fig. 1 indicates that at a dose below the threshold for producing non-specific toxic effects 5-MeODMT significantly and differentially modulates the rewarding and aversive components of lateral hypothalamic ICS. Both latency to initiate ICS and latency to escape ICS at the 0·250 mg kg^{-1} dose are significantly different from baseline ($P < 0.05$, Willcoxon two-tailed signed ranks test). The fact that the two response latencies changed significantly, but in opposite directions, eliminates the possibility that these results were due to either non-specific activation or sedation effects.

The selective increase in escape latencies could be seen as supporting the recent report that 5-hydroxytryptophan (5-HTP) the precursor of 5-HT increases ICS escape latencies in cats (Patkina & Lapin, 1976). However, since 5-HTP may also cause the displacement of catecholamines (German & Bowden, 1974) the findings of Patkina & Lapin (1976) are undoubtedly confounded with concurrent effects on noradrenaline and/or dopamine. This latter explanation is supported by our recent findings (Atrens, Hunt & Becker, in preparation) that the dopamine receptor agonist apomorphine also produces a selective but much larger magnitude increase in escape latencies. That the attenuation of the aversive component of lateral hypothalamic ICS produced by both 5-HTP and 5-MeODMT may be an indirect dopaminergic effect is further supported by the recent report that, in addition to its effects on 5-HT, *NN*-dimethyltryptamine which is closely related to 5-MeODMT, also enhances dopamine release (Waldmeier & Le Maitre, 1977).

The facilitation of reward as indicated by decreased latencies to initiate ICS produced by 5-MeODMT is likely due to its effect on 5-HT. Since 5-MeODMT has both presynaptic and postsynaptic effects (Aghajanian & Haigler, 1975), the question remains whether the reward enhancement represents a presynaptic or postsynaptic effect. To attribute the reward enhancement to its action as a postsynaptic 5-HT agonist has some intuitive appeal since it is widely held that increasing transmitter availability should enhance reward. However, several recent reports (Hunt & others, 1976; Atrens & others, 1977; Franklin & Herberg, 1977) have suggested that this assumption requires an important qualification. That is, a variety of agents which increase transmitter availability in a manner independent of presynaptic activity effectively render the self-stimulation response superfluous and consequently attenuate self-stimulation. These considerations suggest that the reward-enhancement produced by 5-MeODMT reflects an effect on presynaptic 5-HT neurons. Thus these data are consistent with recent reports that, like noradrenaline, 5-HT is an excitatory transmitter with respect to lateral hypothalamic reward processes.

This study was supported by ARGC grant 72/15152 to D. M. Atrens and G. Paxinos.

November 4, 1977

REFERENCES

AGHAJANIAN, G. K. & HAIGLER, H. J. (1975). *Psychopharmac. Commun.*, **1**, 619–629.
ATRENS, D. M. & BECKER, F. T. (1975). *Psychopharmac.*, **44**, 159–163.
ATRENS, D. M., UNGERSTEDT, U. & LJUNGBERG, T. (1977). *Ibid.*, **52**, 177–180.
FRANKLIN, K. B. J. & HERBERG, L. J. (1977). *Eur. J. Pharmac.*, **43**, 33–38.
GERMAN, D. C. & BOWDEN, D. M. (1974). *Brain Res.*, **73**, 381–419.
HUNT, G. E., ATRENS, D. M., CHESHER, G. B., BECKER, F. T. (1976). *Eur. J. Pharmac.*, **37**, 105–111.
KATZ, R. J. & CARROLL, B. J. (1977). *Psychopharmac.*, **51**, 189–193.
KONIG, J. F. R. & KLIPPEL, R. A. (1963). *The rat brain. A stereotaxic atlas of the forebrain and lower parts of the brain stem.* Baltimore: Williams and Wilkins.
MILIARESSIS, E., BOUCHARD, A. & JACOBOWITZ, D. M. (1975). *Brain Res.*, **98**, 194–201.
PATKINA, N. A. & LAPIN, I. P. (1976). *Pharmac., Biochem., Behav.*, **5**, 241–245.
PHILLIPS, A. G., CARTER, D. A. & FIBIGER, H. C. (1976). *Psychopharmac.*, **49**, 23–27.
POSCHEL, B. P. H. & NINTEMAN F. W. (1971). *Physiol. Behav.* **7**, 39–46.
TRULSON, M. E. & JACOBS, B. L. (1976). *Eur. J. Pharmac.*, **36**, 149–154.
WALDMEIER, P. C. & Le MAITRE, L. (1977). *Psychopharmac.*, **52**, 137–144.

Biological effect of phytonadione administered orally as oily solution or solubilized with a non-ionic surfactant in rats

K. THOMA*, G. PFAFF, K. QUIRING†, *Institut fur Galenische Pharmazie der Johann Wolfgang Goethe- Universität Frankfurt am Main, Germany*

It has been shown by Levy & Reuning (1964) and by Anello & Levy (1969) that the bioavailability of solubilized drugs may be determined by the concentrations of free drug molecules in the aqueous phase. On the other hand, Sobel (1952) and Engel & Riggi (1969) provided evidence for an increase of drug absorption when surface-active agents were used. In work from our laboratory (Thoma, Ullman & Fickel, 1970) the distribution of drug molecules between the aqueous and micellar phases was found to be critical for the efficiency of preserving agents; more recent studies have revealed that the changes in photostability observed in solubilized drugs like, e.g., menadione have to be ascribed to the micellar binding of the drug (Thoma & Pfaff, 1976). In our present experiments fatty acid esters of polyoxyethyleneglyceryl have been used.

So far there is limited knowledge about the effects of fatty acid esters of polyoxyethyleneglyceryl on the absorption of drugs with low solubility in aqueous media. In contrast to other lipid-soluble vitamins, only few data are available on the bioavailability of phytonadione (phytomenadione) (see Lowenthal & Taylor, 1959); obviously, studies on the effects of solubilizing compounds on the gastrointestinal absorption of this highly lipophilic vitamin have not yet been made. This led us to investigate the effect of polyoxyethylene-(20)glyceryloleate on the biological effect of phytonadione; neutral oil was used as reference formulation. As a measure of activity the antagonistic effect of phytonadione on the warfarin-produced increase in prothrombin time (Lowenthal & Taylor, 1959) was determined. In this experimental model (1/prothrombin time) *vs* (log phytonadione dose) is linear. Warfarin-pretreated male Wistar rats (150 to 180 g) were used. The substances used were: warfarin-sodium (Merell-Pharma, Gross-Gerau) and vitamin K_1 (phytonadione) (Hoffmann-La Roche, Grenzach); Miglyol 812 Neutralöl (Dynamit Nobel, Witten); calcium-thromboplastin (Behringwerke, Marburg); polyoxyethylene(20)-glyceryloleate (Th. Goldschmidt AG, Essen). Phytonadione was thoroughly mixed with the surfactant and the required amount of water added slowly.

Treatment schedule. The animals were treated with warfarin-sodium (10 mg kg^{-1}, i.p.) 24 h before the administration of phytonadione and fasted for the rest of the experimental period. An interval of 24 h is recommended since the warfarin effect reaches a plateau after 24 h and only slight changes are observed between 24 and 48 h (Niedner, Kayser & Meyer, 1974). After 24 h, phytonadione (30 mg kg^{-1}) was administered by stomach tube (1·0 ml/100 g body weight).

For the preparation of samples, the animals were anaesthetized with ether and blood was withdrawn by cardiac puncture into a plastic syringe containing 1/10 volume of citrate-citric acid buffer (0·1 M, pH 4·8). The samples were cooled to 4°, centrifuged at 2000 *g* and 4° for 15 min (plastic tubes) and kept at 4°.

* Correspondence.
† Present address: Zentrum der Pharmakologie, Klinikum der Universität, D-6000 Frankfurt 70, Germany.