effect. The ratio of an initial increase in perfusion pressure to the remaining increase measured at the end of the infusion period was considered as an index of acute tolerance to NE. In 11 experiments the percent of the increase in initial perfusion pressure was 67 ± 9%, and the index of acute tolerance was 1.54 ± 0.16 (mean ± SEM). At the time of an infusion, there appeared in the effluent a substance contracting the chick rectum and rat colon (Figure). On the basis of differential sensitivity of both organs to different types of PG, it could be suspected that there was released a PGE-like material. Its peak concentration in the effluent in terms of PGE_2-like activity was 5.08 ± 0.72 ng/ml (9 experiments). If a PGF-like substance was released into the effluent, then its concentration had to be lower than 0.5 ng/ml. Infusions of NE at a concentration higher than 300 ng/ml sometimes produced an appearance of PGF-like material in the effluent, but then no acute tolerance of pressor response was observed.

The prostaglandin character of the released substance was confirmed by the pretreatment of the ear vessels with an inhibitor of PG biosynthesis-indomethacin (3 µg/ml). In the presence of indomethacin NE did not release a substance contracting the assay organs (8 experiments, Figure), but an initial increase in perfusion pressure was the same as in control experiments (69 ± 8%), while the index of acute tolerance was significantly lower (1.05 ± 0.04, $p < 0.01$) than in control experiments. The pretreatment of the ear vessels with phenoxybenzamine, but not with propranolol (6 experiments) completely blocked the pressor response to NE, and then there was no release of PGE-like substance into the effluent.

Therefore we assume that contracting vascular wall produces PGE, which are responsible for acute tolerance to NE. Many authors[9,13,14] have demonstrated that exogenous PGE diminish the vasoconstrictor action of NE. There is also indirect evidence that the intramural generation of PGE in blood vessels may be a feedback mechanism limitting vasoconstrictor action of catecholamines[9,15] or angiotensin[10]. Our data support this concept.

Zusammenfassung. Durch Noradrenalin ausgelöste Vasokonstriktion am perfundierten Kaninchenohr ist begleitet von der Freisetzung eines PGE-ähnlichen Stoffs, welcher für die Entwicklung der akuten Toleranz gegenüber der vasokonstriktorischen Wirkung von Noradrenalin verantwortlich ist.

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[13] J. Nakano, in *The Prostaglandins* (Ed. P. W. Ramwell, Plenum Press, New York, London 1973), vol. 1, p. 239.
[14] P. J. Kadowitz, C. S. Sweet and M. J. Brody, J. Pharmac. exp. Ther. *177*, 641 (1971).
[15] H. Janczewska and K. Herbaczyńska-Cedro, Pol. J. Pharmac. Pharm. *26*, 159 (1974).
[16] The authors gratefully acknowledge the supply with prostaglandins by Dr J. Pike, Upjohn Co, Kalamazoo, USA.

Stimulation of Sexual Behaviour in Rats by a Benzodioxane Derivative

In the course of screening potential centrally acting muscle relaxants, it was noticed by Morrison[1] that young adult male Wistar rats which were housed in groups of 10 showed unusually excited sexual behaviour some hours after the administration of a benzodioxane derivative, 2-(3′*tert*-amylsulphonylpropyl)aminoethyl-1:4-benzodioxane (WB 4371) (Figure 1). Effects of this kind have previously been shown mainly with hormones and with *p*-chlorophenylalanine (pCpA), and recently also with L-dopa[2]. Benzodioxanes have hitherto been regarded as predominantly hypotensive and/or CNS depressant.

Pilot experiments were also carried out with a number of other benzodioxane derivatives, but WB 4371 was found to be the most potent of the series in stimulating sexual activity. Experiments were therefore done to quantify and analyze these effects, and also to compare WB 4371 with pCpA which has been reported, for example, to enhance sexual behaviour in male rats[3–7] and in cats of both sexes[6–9], though opposite effects have also been shown[10].

All experiments were carried out with naive adult male Wistar rats (200–250 g) which had been housed in standard conditions in large cages containing 12 rats each. All injections were i.p. and WB 4371 was dissolved and pCpA was suspended in 1% Tween 80. Observations of sexual activity were made 4 to 5 h after injection with WB 4371, so as to allow its initial CNS depressant effects to wear off, and 6 h after injection with pCpA, to allow its sedative effects to wear off. Rats were tested in an observation cage in groups of 4, each animal having received the same treatment. The sexual acts scored were similar to those described by Grant and McIntosh[11]. All tests lasted 15 min and took place in the afternoon. For practical reasons the rats were not kept in a reversed day/night light cycle.

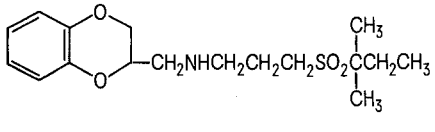

Fig. 1. Chemical structure of benzodioxane derivative WB 4371.

[1] P. Morrison, unpublished results.
[2] M. Da Prada, M. Carruba, A. Saner, R. A. O'Brien and A. Pletscher, Brain Res. *55*, 383 (1973).
[3] E. E. Shillito, Br. J. Pharmac. *36*, 193 (1969).
[4] E. E. Shillito, Br. J. Pharmac. *38*, 305 (1970).
[5] A. Tagliamonte, P. Tagliamonte, G. L. Gessa and B. B. Brodie, Science *166*, 1433 (1969).
[6] C. O. Malmnäs and B. J. Meyerson, Nature, Lond. *232*, 398 (1971).
[7] P. J. Salis and D. A. Dewsbury, Nature, Lond. *232*, 400 (1971).
[8] J. Ferguson, S. Henriksen, M. Cohen, G. Mitchell, J. D. Barchas and W. C. Dement, Science *170*, 499 (1970).
[9] V. J. Hoyland, E. E. Shillito and M. Vogt, Br. J. Pharmac. *40*, 659 (1970).
[10] A. Zitrin, F. A. Beach, J. D. Barchas and W. C. Dement, Science *170*, 868 (1970).
[11] E. C. Grant and J. H. McIntosh, Behaviour *21*, 246 (1963).

In the first set of experiments rats were given a single injection of either 20 or 40 mg/kg of WB 4371. A slight but non-significant increase in the number of male to male sexual acts as compared with saline controls was observed. Next, 5 different doses of WB 4371 were injected daily for 4 days, and the dose response curve (Figure 2) shows that the maximum effect of WB 4371 occurred at 40 mg/kg ($p < 0.04$; Mann-Whitney U-test). The maximum response at 40 mg/kg may be related to the fact that at the time of testing these rats had clearly recovered from the sedative effect of the drug, whereas with both of the higher doses they still appeared sedated.

In order to compare WB 4371 with pCpA, rats were assigned at random to 1 of 3 treatments; 100 mg/kg pCpA, 40 mg/kg WB 4371 and 1% Tween 80 (control group). The dose of pCpA was chosen because it has been shown to give maximal effects[5]. pCpA and WB 4371 produced approximately 3 and 4 times the number of sexual acts respectively compared with the controls (Figure 3). The difference between the Tween 80 and the drug tested rats was significant ($p < 0.01$ in both cases).

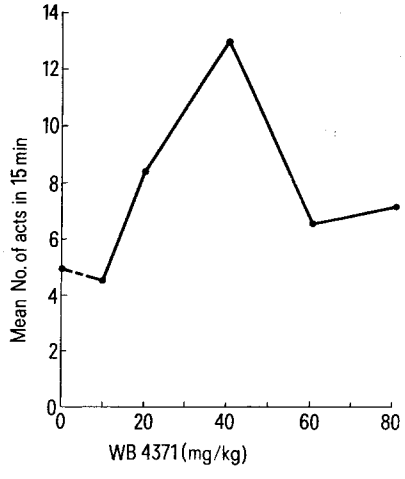

Fig. 2. Effects of several doses of WB 4371 on sexual behaviour between Male Wistar rats. The animals were pre-treated for 4 days prior to testing. Both 40 mg/kg and 80 mg/kg WB 4371 produced significant increases in sexual activity ($p < 0.04$ and 0.02 respectively, $n = 8$ per group).

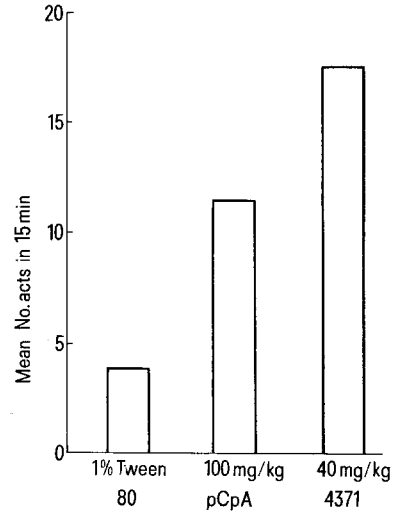

Fig. 3. Comparison between the effect of 40 mg/kg WB 4371 and 100 mg/kg pCpA given daily for 4 days, on sexual behaviour among Wistar rats. Both drugs produced marked increases in sexual activity ($n = 8$ per group).

The possibility that the hypersexual behaviour of the WB 4371 treated rats was merely a reflection of an increase in general spontaneous activity was investigated by means of a Y-maze test similar to that described by STEINBERG et al.[12]. The animals were placed singly in a Y-shaped runway for a period of 3 min and the number of entries into the arms of the runway and the number of rears onto the hindlegs was scored. Rats were injected with saline and with WB 4371, 20, 40, 60 or 80 mg/kg daily for 4 days and were tested 4 h after the last dose. No significant change was found in the number of entries of the treated animals. The number of rears was slightly reduced by all the doses of WB 4371 ($F = 3.7$; $p < 0.01$).

As the previous experiments had been carried out with males only, it was decided to investigate the effect of WB 4371 on heterosexual behaviour. Two preliminary 'selection' tests were carried out, 4 days apart, with 96 male rats: 2 untreated males at a time were placed with 2 hooded female rats in an observation cage, and the number of sexual acts during 10 min was recorded. On the basis of results obtained in these tests it was possible to classify the males into 2 groups. Rats which gave a mean score of 0 to 4.5 were assigned to a 'low activity' group and those with a mean score of above 11 were placed in a 'high activity' group. Animals with a mean score of between 4.5 and 11 were excluded from the experiment, thus dividing the remainder into 2 distinct groups. In this way, a total of 84 males was available. The high and low activity groups were subdivided and given either saline, pCpA (100 mg/kg), or WB 4371 (40 mg/kg) for 4 days, making 14 per sub-group. Tests were repeated, and the number of sexual acts for the drug treated males in the 'high activity' groups was virtually unchanged and was similar to that of the controls (Figure 4). The mean scores of the 'low activity' groups were significantly increased for both drugs over their pretreatment values ($p < 0.01$; Wilcoxon matched-pairs test; $n = 14$ per group). WHALEN and LUTTGE[13] have reported that pCpA did not enhance sexual interactions between known sexually vigorous males and female rats, and MALMNÄS and MEYERSON[6], using castrated males which had been maintained on a sub-maximal dose of testosterone, found that it did. Our results would seem consistent with these findings, in that rats which showed a 'normal' level of heterosexual behaviour did not increase their scores with either pCpA or WB 4371, but rats which had a naturally low level of heterosexual activity were markedly stimulated.

In view of the stimulant effect of WB 4371 on sexual behaviour it was decided to investigate whether it was blocked by 5-hydroxytryptophan (5-HTP). 3 groups of male rats given either 1% Tween 80, 100 mg/kg pCpA or 40 mg/kg WB 4371 daily for 4 days, were subdivided on the 4th day and given 1% Tween 80 or 10 mg/kg 5-hydroxy-tryptophan[4] 1 h before being tested with female rats. 5-HTP appeared to block the sexual activity produced by WB 4371 as well as that produced by pCpA (Figure 5). Both WB 4371 + 1% Tween 80 and pCpA + 1% Tween 80 treated rats gave significantly increased scores

[12] H. STEINBERG, R. RUSHTON and C. TINSON, Nature, Lond. *192*, 533 (1961).

[13] R. E. WHALEN and W. G. LUTTGE, Science *169*, 1000 (1970).

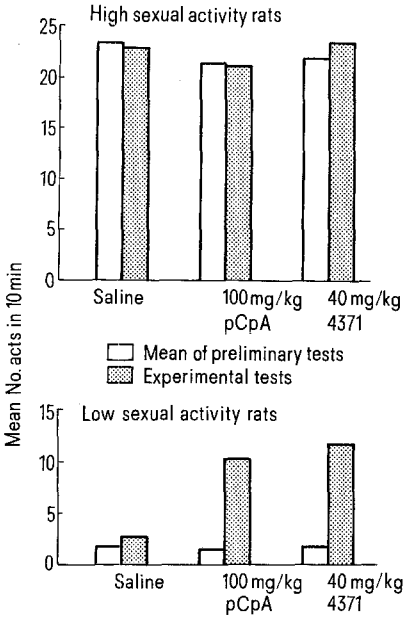

Fig. 4. Effects of 40 mg/kg WB 4371 and 100 mg/kg pCpA given daily for 4 days on male Wistar rats previously selected for 'high' or 'low' sexual activity when tested with female rats. The figure shows the results of the selection and the results after 4 days of drug treatment. In this experiment pCpA was suspended in, and WB 4371 was dissolved in, saline instead of Tween 80. Both WB 4371 and pCpA significantly increased the amount of sexual behaviour towards female rats by the 'low' activity groups ($p < 0.01$ in each case), but had little or no effect on the 'high' activity groups ($n = 14$ per group).

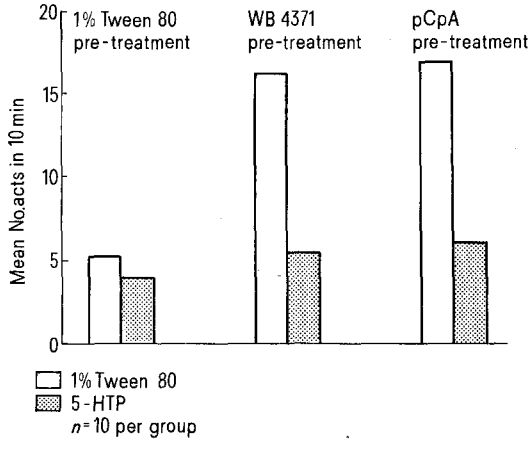

Fig. 5. Effects of 10 mg/kg 5-hydroxytryptophan (5-HTP) or 1% Tween 80 on the sexual behaviour of male Wistar rats pre-treated with either 1% Tween 80, 40 mg/kg WB 4371 or 100 mg/kg pCpA daily for 4 days. The dose of 5-HTP or 1% Tween 80 was administered i.p. 1 h before testing. Both WB 4371 + 1% Tween 80 and pCpA + 1% Tween 80 treated rats gave significantly increased scores ($p < 0.02$ in both cases) but the WB 4371 + 5-HTP and the pCpA + 5-HTP treated animals were not significantly different from controls ($n = 10$ per group).

($p < 0.02$ in both cases) but the WB 4371 + 5-HTP and pCpA + 5-HTP treated animals were not significantly different from controls. There were 10 rats in each group.

The action of pCpA is thought to be related to a decrease of brain 5-HT which results from an inhibition of tryptophan hydroxylase. It has also been suggested that a relative imbalance of cerebral catecholamines and of 5-HT might be involved (TAGLIAMONTE et al.[5]). The case for the paramount importance of lowered cerebral 5-HT levels in the stimulation of sexual behaviour has been vigorously argued by DA PRADA et al.[14,15,2], and it would be especially interesting in view of our last finding to study what, if any, effects WB 4371 has on this amine[16].

Zusammenfassung. Nachweis, dass ein bestimmtes Benzodioxanderivat (WB 4371) eine ausgeprägte Steigerung des Sexualverhaltens männlicher Ratten bewirkt, insbesondere bei Tieren mit geringer sexueller Aktivität. Die stimulierenden Effekte von WB 4371 waren mindestens so stark wie pCpA und wurden wie bei pCpA selbst durch 5-HTP blockiert.

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[14] M. DA PRADA, M. CARRUBA, R. A. O'BRIEN, A. SANER and A. PLETSCHER, Eur. J. Pharmac. *19*, 288 (1972).

[15] M. DA PRADA, M. CARRUBA, A. SANER, R. A. O'BRIEN and A. PLETSCHER, *Psychopharmacology, Sexual Disorders and Drug Abuse* (Ed. T. A. BAN, North Holland Publishing Co. Amsterdam-London 1973), p. 517.

[16] We thank Drs M. BESSER and D. H. JENKINSON and Professor H. O. SCHILD for helpful comments, and Mr. D. P. BLUNDELL for help with the experiments.

[17] Reprints by Prof. HANNAH STEINBERG, Pharmacology Department, University College London, Gower Street, London, WC1E 6BT (England).

The Behavioral Effects of 2,5-Dimethoxy-4-Alkyl Amphetamines

The hallucinogenic derivatives of tryptamine and phenylalkylamine show cross tolerance with lysergic acid diethylamide (LSD) indicating that they share a common mode of action[1]. The A ring of LSD could correspond to the 6-membered rings of tryptamine and phenethylamine. The N(6) of LSD is probably located at the position of the side-chain nitrogen in the tryptamine and phenethylamine moieties (Figure 1). This hypothesis as propounded by KANG and GREEN[2] has been supported by a variety of experimental findings. As would be predicted from this theory the *trans* isomer of 2-(3,4,5-trimethoxyphenyl) cyclopropylamine appears to have the biological activity of mescaline[3]. The rigid analogues 2-amino-7-hydroxy-

[1] P. BRAWLEY and J. C. DUFFIELD, Pharmac. Rev. *24*, 31 (1972).

[2] S. KANG and J. P. GREEN, Proc. natn. Acad. Sci., USA *67*, 62 (1970).

[3] P. D. COOPER and G. C. WALTERS, Nature New Biol. *238*, 96 (1972).