REFERENCES

GIBALDI, M. & NIGHTINGALE, C. H. (1968). *J. pharm. Sci.*, **57**, 1354–1357.
HELENIUS, A. & SIMONS, K. (1972). *J. biol. Chem.*, **247**, 3656–3661.
KAKEMI, K., SEZAKI, H., KONISHI, R., KIMURA, T. & MURAKAMI, M. (1970). *Chem. Pharm. Bull.*, **18**, 275–280.
KIMURA, T., SEZAKI, H. & KAKEMI, K. (1972). *Ibid.*, **20**, 1656–1662.
MAKINO, S. REYNOLDS, J. A. & TANFORD, C. (1973). *J. biol. Chem.*, **248**, 4926–4932.
MARRIOTT, C. & KELLAWAY, I. W. (1976). *J. Pharm. Pharmac.*, **28**, 620–624.
MAYERSOHN, M., FELDMAN, S. & GIBALDI, M. (1969). *J. Nutrition*, **98**, 288–296.
NIGHTINGALE, C. H., WYNN, R. J. & GIBALDI, M. (1969). *Ibid.*, **58**, 1005–1007.
NORMAN, A. (1960). *Acta chem. scand.*, **14**, 1295–1299.
PHILIPPOT, J. (1971). *Biochim. biophys. Acta*, **225**, 201–213.
PURDON, A. D., TINKER, D. O. & NEUMANN, A. W. (1976). *Chem. Phys. Lipids*, **17**, 344–352.
ROBINSON, N. & SAUNDERS, L. (1958). *J. Pharm. Pharmac.*, **10**, 755–761.
TANFORD, C., NOZAKI, Y., REYNOLDS, J. A. & MAKINO, S. (1974) *Biochemistry*, **11**, 2369–2376.

Concentration of prolactin in serum of rats treated with baclofen

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Baclofen (Lioresal) has central depressant properties which are useful for the control of spasticity (Jones, Burke & others, 1970). The drug also appears to act like γ-hydroxybutyric acid and γ-butyrolactone to inhibit the firing of dopaminergic nerves in the nigrostriatal and mesolimbic neuronal systems, as evidenced by the ability of these drugs to block neuroleptic-induced increase of dopamine turnover (Fuxe, Hökfelt & others, 1975) and increase the concentration of dopamine in brain regions innervated by these neurons (Da Prada & Keller, 1976; Kelly & Moore, 1976; Gianutsos & Moore, 1977). To determine if baclofen has a similar action on dopamine neurons in the tuberoinfundibular system, the effects of this drug on serum prolactin concentrations was determined. Secretion of prolactin is tonically inhibited by tuberoinfundibular dopaminergic neurons so that drugs which interfere with the activity or actions of these neurons should cause the concentration of prolactin in the serum to increase (MacLeod, 1974).

Adult male Sprague-Dawley rats, 200–250 g, received injections of various doses of baclofen or saline vehicle intraperitoneally and were decapitated 1 h later. Blood collected from the trunk was centrifuged and serum stored at −20° until assayed for prolactin by the double antibody radioimmunoassay described by Niswender, Chen & others (1969). Values are expressed in terms of NIAMDD-rat prolactin-PR-1.

Baclofen at 5 and 10 mg kg^{-1} slightly reduced, but at 20 mg kg^{-1} markedly increased the serum concentration of prolactin. Since the animals are anaesthetized at the higher dose, and appear to have respiratory difficulties, the effect on prolactin may be unrelated to a specific action of the drug on tuberoinfundibular neurons, but rather to a non-specific stress-induced effect. Many types of stressful situations increase serum prolactin concentrations (Neill, 1974).

Neuroleptics increase serum concentrations of prolactin (Dickerman, Clark & others, 1972; Clemens, Smalstig & Sawyer, 1974), presumably due to their ability to block dopamine receptors. Fredericksen (1975) reported that baclofen is effective in treating some schizophrenics and may enhance the antipsychotic effects of neuroleptics, although others have been unable to confirm these effects (Simpson, Branchey & Shrivastava, 1976). Nevertheless, it was of interest to determine if baclofen enhanced the prolactin elevating action of neuroleptics. For this purpose, a dose of haloperidol which has been shown to be at the threshold for increasing serum prolactin concentrations (Mueller, Simpkins & others, 1976) was administered 2 h before the administration of a range of doses of baclofen having no influence on prolactin concentrations. It was postulated that the two drugs, acting together, would increase the serum concentration of prolactin, but as summarized in Table 1, this was not so. Haloperidol (0·03 mg kg^{-1}) pretreatment produced a slight increase in the circulating prolactin concentrations. In vehicle-pretreated rats 10 mg kg^{-1} or less of baclofen did not increase prolactin concentrations, confirming the results in Fig. 1. When increasing doses of baclofen were administered to rats pretreated with haloperidol the serum prolactin concentrations were not significantly different from values in animals pre-treated with the haloperidol vehicle.

Since non-anaesthetic doses of baclofen did not increase serum prolactin concentrations in the first experiment and since baclofen did not enhance the effects of haloperidol on prolactin concentrations in the second experiment, it would appear that, at least in non-anaesthetic doses, baclofen does not inhibit the firing of

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Table 1. *Effects of haloperidol pretreatment on prolactin concentrations in rats treated with baclofen.* Rats were pretreated with haloperidol (0·03 mg kg^{-1}, s.c.) or vehicle (0·3% tartaric acid) 2 h before intraperitoneal injections of baclofen or saline (zero dose). Rats were killed 1 h after baclofen. Numbers represent mean ± 1 s.e. of the prolactin concentration (ng ml^{-1}) in the serum from 7–8 animals. The prolactin concentrations in serum of animals treated with baclofen were not significantly different from the appropriate zero dose controls at the 1% level (Student's *t*-test).

Dose of baclofen (mg kg^{-1})	Pretreatment	
	Vehicle	Haloperidol
0	11 ± 2	17 ± 3
0·1	10 ± 1	22 ± 3
0·3	12 ± 1	14 ± 1
1	11 ± 1	13 ± 1
3	7 ± 1	11 ± 1
10	7 ± 1	13 ± 2

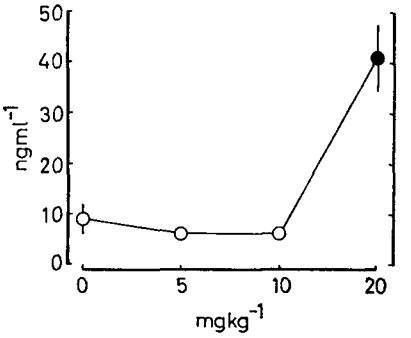

FIG. 1. Effect of baclofen (mg kg^{-1}) on the concentration of prolactin (ng ml^{-1}) in rat serum. Rats received intraperitoneal injections of saline or baclofen and were killed 1 h later. Each symbol represents the mean and the verticle line ± 1 s.e. from 8 determinations. Where not shown the s.e. is less then the radius of the symbol. ●—significantly different at the 1% level from zero dose (saline), Student's *t*-test.

tuberoinfundibular neurons. Baclofen, like γ-butyrolactone, inhibits the impulse traffic in nigrostriatal and mesolimbic dopaminergic neurons as evidenced by direct electrical recording (Bernard, Edwards & others, 1975; Dray & Staughan, 1976) and by the increase in the dopamine in the terminals of these neurons (e.g., Da Prada & Keller, 1976; Kelly & Moore, 1976). On the other hand, neither baclofen nor γ-butyrolactone increases the dopamine concentration in the median eminence which contains the terminals of the tuberoinfundibular neurons (Gudelsky & Moore, 1976; Moore & Gudelsky, 1977).

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REFERENCES

BERNARD, P., EDWARDS, S. J., FIELDING, S., ROBSON, R. D., SAELENS, J. K., SIMKE, J. P. & WELCH, J. (1975). *Pharmacologist*, **17**, 256.

CLEMENS, J. A., SMALSTIG, E. G. & SAWYER, B. D. (1974). *Psychopharmacologia*, **40**, 123–127.

DA PRADA, M. & KELLER, H. H. (1976). *Life Sci.*, **19**, 1253–1264.

DICKERMAN, S., CLARK, J., DICKERMAN, E. & MEITES, J. (1972). *Neuroendocrinology*, **9**, 332–340.

DRAY, A. & STRAUGHAN, D. W. (1976). *J. Pharm. Pharmac.*, **28**, 400–405.

FREDERIKSEN, P. K. (1975). *Lancet*, **1**, 702–703.

FUXE, K., HÖKFELT, T., LJUNGDAHL, A., AGNATI, L., JOHANSSON, O. & PEREZ DE LA MORA, M. (1975). *Med. Biol.*, **53**, 177–183.

GIANUTSOS, G. & MOORE, K. E. (1977). *Psychopharmacology*, **51**, in the press.

GUDELSKY, G. A. & MOORE, K. E. (1976). *J. Neural Trans.*, **38**, 95–105.

JONES, R. F., BURKE, D., MAROSSZEKY, J. E. & GILLES, J. D. (1970). *J. Neurol Neurosurg. Psychiat.*, **33**, 464–468.

KELLY, P. H. & MOORE, K. E. (1976). *Pharmacologist*, **18**, 130.

MACLEOD, R. M. (1974). *Mammary Cancer and Neuroendocrine Therapy*, pp. 139–159, London: Butterworths.

MOORE, K. E. & GUDELSKY, G. A. (1977). *Ad. Biochem. Psychopharmac.*, **16**, 227–235.

MUELLER, G. P., SIMPKINS, J., MEITES, J. & MOORE, K. E. (1976). *Neuroendocrinology*, **2**, 121–135.

NEILL, J. D. (1974). In: *Handbook of Physiology*, Section 7, *Endocrinology*, Vol. IV, Part 2, pp. 469–488. Editors: Greep, R. O. and Astwood, E. B., Baltimore; Williams and Wilkins.

NISWENDER, G. D., CHEN, C. L., MIDGELY, A. R., MEITES, J. & ELLIS, S. (1969). *Proc. Soc. exp. Biol. Med.*, **130**, 793–797.

SIMPSON, G. M., BRANCHEY, M. H. & SHRIVASTAVA, R. K. (1976). *Lancet*, **1**, 966–967.