Physical performance of mice treated with propranolol, sotalol and INPEA

I have made a comparative study of the behavioural effects of three adrenergic β-receptor blocking drugs frequently used in animal experiments.

Adult NMRI mice of either sex were allowed free access to a standard diet (Altromin R) and tap water and were housed at 25°. They were treated intraperitoneally with (±)-propranolol hydrochloride (±)-sotalol [4-(isopropylamino-1-hydroxyethyl) methane sulphonanilide HCl] or D-(−)-INPEA [1-(4′-nitrophenyl)-2-isopropylamino-ethanol HCl].

Spontaneous motor activity of single mice was recorded for 2 h in circular activity cages (Estler & Ammon, 1969) immediately after application of the drugs. Spontaneous orientational hypermotility of single mice was measured in the Basile activity cage (Estler & Ammon, 1969) for 15 min starting 30 min after the application of the drugs. Sedation or ataxia was tested on a sloping plane. The principle of this test was modified in such a way that quantitative data could be obtained. For this purpose the animals were placed on a small board which could be turned slowly from a horizontal to a vertical plane. The angle at which the animals could no longer cling to the board was registered, This test was made 45 min after administration of the drugs. The traction test (Julou, 1956), which also gives a measure for sedation or ataxia was used 45 min after injection of the drugs.

Mean values from 20–24 single determinations showed that propranolol (1, 5 and 20 μg/g) and sotalol (1·5 and 25 μg/g) did not change the spontaneous motor activity of mice, when compared with saline treated controls INPEA) 5 and 25 μg/g), was likewise ineffective, bnt at 100 μg/g it increased the motility by 60–230%. The maximum effect was seen 60 min after drug administration.

Orientational hypermotility was depressed by 1,5 and 20 μg/g of propranolol ($P < 0{\cdot}05$). Lower doses were ineffective. Sotalol had a biphasic effect: 0·05 and 0·2 μg/g slightly increased and 25 μg/g reduced the hypermotility. INPEA was ineffective at all doses (0·01–100 μg/g). (Results were from 20 single determinations).

Propranolol (0·01–20 μg/g) and sotalol (0·01–25 μg/g) did not affect the behaviour of the animals on the sloping plane. INPEA at the highest dose (100 μg/g) slightly but significantly ($P < 0{\cdot}05$) impaired the performance of the animals in this test (68° instead of 76° in the control group). In the traction test 0·01–20 μg/g propranolol and 0·01–25 μg/g sotalol were ineffective. After 100 μg/g of INEPA 90% negative results were recorded as compared with 7% (confidence limits 1–29%) in the control groups. This effect of INPEA must be ascribed to impaired muscular coordination of the exited and hyperactive animals. The lower doses of INPEA (0·01–25 μg/g) were ineffective.

The test for orientational hypermotility, which I found to be the most sensitive test for detecting central depressant properties, showed propranolol, in doses that are known to exert β-adrenergic blocking effects, to have some sedative properties. This agrees with the observations of others: (Leszkovsky & Tardos, 1965, Murmann, Almirante & Saccani-Guelfi, 1966; Estler & Ammon, 1969). INPEA in high doses, on the other hand, shows distinct central stimulating properties, as was also suggested by Murmann & others (1966). In contrast to Lish, Weikel & Dungan (1965) a sedative effect could be seen after 25 μg/g of sotalol, whereas lower doses of this drug appeared to increase orientational hypermotility, an effect just above the significance level ($P = 0{\cdot}05$).

Propranolol was kindly supplied by Dr. H. P. Kuemmerle, Rhein Pharma GmbH, Heidelberg, Germany, INPEA by Dr. W. Murmann, Selvi e C., Milan, Italy, and sotalol by Dr. P. M. Lish, Mead Johnson Res. Ctr., Evansville, Ind., U.S.A.

Pharmakologisches Institut C.-J. ESTLER
der Universität Erlangen-Nürnberg,
Universitätsstrasse, 22,
D-8520 Erlangen, Germany.

April 26, 1971

REFERENCES

ESTLER, C.-J. & AMMON, H. P. T. (1969). *J. Pharm. Pharmac.*, **21**, 554–555.
JULOU, L. (1956), cited by COURVOISIER, S. (1956). *J. clin. exp. Psychopath.*, **17**, 25.
LESZKOVSKY, G. & TARDOS, L. (1965). *J. Pharm. Pharmac.*, **17**, 518–519.
LISH, P. M., WEIKEL, J. H. & DUNGAN, K. W. (1965). *J. Pharm. exp. Ther.*, **149**, 161–173.
MURMANN, W., ALMIRANTE, L. & SACCANI-GUELFI, M. (1966). *J. Pharm. Pharmac.*, **18**, 317–318.

Inhibition of (+)-amphetamine hyperthermia by blockade of dopamine receptors in rabbits

The hyperthermia produced in rabbits by (+)-amphetamine is apparently due to an action of the drug on the CNS (Hill, 1971). Indications for this central action include the findings that (+)-amphetamine hyperthermia in this species is markedly reduced by prior curarization (Belenky & Vitolina, 1962) or spinal section (Hill & Horita, 1970) but is not diminished by blockade of β- or peripheral α-adrenergic receptors (Hill & Horita, 1970). Other evidence suggests that (+)-amphetamine might produce hyperthermia by influencing a central dopaminergic system. For example, several of the neuroleptic drugs antagonize (+)-amphetamine hyperthermia in rats (Morpurgo & Theobald, 1967). These and other neuroleptics were later found to be potent inhibitors of central dopaminergic function (Andén, Butcher & others, 1970). That low doses of (+)-amphetamine can elevate both body temperature and the turnover rate of brain dopamine without altering the turnover rate of brain noradrenaline in the rat further implicates dopamine as the neurochemical concerned in (+)-amphetamine-induced hyperthermia (Costa & Groppetti, 1970).

However, it is difficult to determine from such information whether dopamine receptor activation is necessary for production of hyperthermia by (+)-amphetamine. The neuroleptics employed by Morpurgo & Theobald (1967) are known to also block central and peripheral α-adrenergic receptors (Janssen, Niemegeers & others, 1968; Andén & others, 1970). Further, an increased turnover rate of dopamine does not necessarily imply increased dopamine receptor activation. A more direct means of evaluating the possible involvement of central dopamine receptors in the production of hyperthermia by (+)-amphetamine is to assess the effect of specific dopamine antagonists on this response. Since pimozide* had been shown to selectively inactivate dopamine receptors in the CNS (Andén & others, 1970), the ability of this drug to antagonize (+)-amphetamine hyperthermia was investigated.

Male New Zealand rabbits (1·8–2·0 kg) received an injection of either pimozide or the pimozide solvent (dilute tartaric acid) intraperitoneally 3 h before intravenous injection of (+)-amphetamine or saline. Sedation and catalepsy were evident 30 min after pimozide administration, reached maximal intensity at about 2 h and persisted for more than 12 h in rabbits receiving no (+)-amphetamine. In addition, these animals exhibited marked and continuous miosis. Administration of (+)-amphetamine 3 h after pimozide resulted in a transient increase in pupillary size and motor activity. Sedation, catalepsy, and miosis were again evident 15 min later and persisted for more than 12 h.

* 1-{1-[4,4-bis(*p*-fluorophenyl)butyl]-4-piperidyl}-2-benzimidazolinone.