Effect of drugs that modify 3′,5′-AMP concentrations on morphine analgesia

Several drugs affecting adrenergic transmission mechanisms can modify the responses to nociceptive stimuli and alter the analgesic effect of morphine and related substances (Gross, Holland & others, 1948; Leimdorfer & Metzner, 1949; Muñoz, 1963). Most authors consider this fact an indication that some analgesic agents act through a change of catecholamine concentrations in the central nervous system (cns) (Sigg, Caprio & Schneider, 1958; Frommel, Fleury & Schmidt-Ginzkey, 1963; Contreras & Tamayo, 1966; Muñoz & Paeile, 1967; Maynert, 1967; Contreras, Tamayo & others, 1969). Since it is also accepted that some pharmacological properties of catecholamines are mediated by cyclic 3′,5′-AMP (Sutherland & Rall, 1960), we have examined the interactions of morphine with a number of drugs that affect the cyclic adenylate concentrations.

Female albino mice, 28–33 g, were placed on a hot plate at 54° ± 0·5° before and at 30, 60, 90 and 120 min after the administration of drugs according to Woolfe & MacDonald (1944). Results are expressed as the mean of the maximum effect and as the area under the time response curve formed by plotting the increase in the reaction time (licking forepaws or a sudden jump) on the ordinate and the time intervals after drug administration on the abscissae (Winter & Flataker, 1950). The drugs employed were: morphine, theophylline, imidazole, sodium fluoride and propranolol. Morphine and saline were injected subcutaneously, the other compounds were administered intraperitoneally.

The effects of drugs that change cyclic 3′,5′-AMP concentrations are shown in Table 1. A significant decrease in the maximum effect was observed in mice treated with theophylline and propranolol, while no significant changes were observed in the area. In contrast, imidazole increased the reaction time to significant levels (as measured by the *t*-test) at the dose of 150 mg/kg. Imidazole produced this effect accompanied by excitement and increased aggressiveness of animals. Sodium fluoride did not significantly affect morphine analgesia. The combined effects of morphine and other drugs are summarized in Table 2. Propranolol and imidazole significantly increased the effect of morphine, the other compounds were ineffective.

Catecholamines stimulate the formation of cyclic 3′,5′-AMP in several tissues including the cns (Sutherland, Rall & Menon, 1962; Klainer, Chi & others, 1962). Theophylline and sodium fluoride allow an accumulation of the cyclic adenylate by inhibiting phosphodiesterase and activating adenylcyclase, respectively (Sutherland

Table 1. *Effects of theophylline, imidazole, sodium fluoride and propranolol on the reaction to thermal stimulus in mice.*

Drug, mg/kg	Effect	
	Max. change (Mean ± s.e.)	Area (Mean ± s.e.)
Saline	0·9 ± 0·5	36·6 ± 46·2
Theophylline, 10	−1·0 ± 0·5*	−67·8 ± 50·4
Theophylline, 15	−1·0 ± 0·52*	−66·0 ± 49·8
Imidazole, 100	2·6 ± 0·75	195·0 ± 68·4
Imidazole, 150	4·2 ± 1·21*	415·8 ± 91·8**
Sodium fluoride, 10 ..	1·8 ± 0·95	146·4 ± 57·0
Propranolol, 5	−0·9 ± 0·74***	−25·2 ± 54·6
Propranolol, 10	1·3 ± 0·41	26·4 ± 70·8

* $P<0·02$. ** $P<0·001$. *** $P<0·05$. No. of mice: 15 per group.

Table 2. *Effect of theophylline, imidazole, sodium fluoride and propranolol on the analgesic response to morphine in mice.*

Drug, mg/kg	Effect	
	Max. change (Mean ± s.e.)	Area (Mean ± s.e.)
Morphine, 5	12·1 ± 1·44	921·6 ± 101·4
Theophylline, 10 + morphine, 5 ..	12·2 ± 1·72	851·4 ± 127·8
Theophylline, 15 + morphine, 5 ..	13·5 ± 1·18	1004·4 ± 66·6
Imidazole, 100 + morphine, 5	13·8 ± 1·24	1307·4 ± 96·0*
Imidazole, 150 + morphine, 5	17·6 ± 0·92**	1537·2 ± 96·0***
Sodium fluoride, 10 + morphine, 5 ..	12·3 ± 1·44	1066·2 ± 102·6
Propranolol, 5 + morphine, 5	13·1 ± 1·17	1344·0 ± 103·8*
Propranolol, 10 + morphine, 5	14·7 ± 1·30	1215·6 ± 135·6

* $P<0.01$. ** $P<0.005$. *** $P<0.001$. No. of mice: 20 per group.

& others, 1962). Imidazole induces the opposite effect in that it stimulates phosphodiesterase (Butcher & Sutherland, 1962) and propranolol blocks the adenylcyclase (Robison, Butcher & Sutherland, 1967). The present experiments do not provide evidence in favour of the assumption that morphine analgesia is mediated by an increase in 3′,5′-AMP concentrations, since no significant results were observed after theophylline or sodium fluoride administration, whereas imidazole, which decreases the adenylate concentrations, exhibited a synergistic action with morphine. However, negative results obtained do not discard a possible relation of morphine analgesia with cyclic AMP, since the drugs used in conjunction with morphine have many other effects that may induce concomitant changes in animal reactions to painful stimuli.

Department of Pharmacology,
University of Concepción,
Cassilla 74-C,
Concepción, Chile.

E. CONTRERAS
S. CASTILLO
L. QUIJADA

September 2, 1971

REFERENCES

BUTCHER, R. W. & SUTHERLAND, E. W. (1962). *J. biol. Chem.*, **237**, 1244–1250.

CONTRERAS, E. & TAMAYO, L. (1966). *Archs int. Pharmacodyn. Thér.*, **160**, 312–320.

CONTRERAS, E., TAMAYO, L., PINCHEIRA, Y. & QUIJADA, L. (1969). *Ibid.*, **179**, 452–458.

GROSS, E., HOLLAND, H., CARTER, H. R. & CHRISTENSEN, E. M. (1948). *Anesthesiology*, **9**, 459–471.

FROMMEL, E., FLEURY, C. & SCHMIDT-GINZKEY, J. (1963). *Medna Pharmac. exp.*, **8**, 171–175.

KLAINER, L. M., CHI, Y. M., FREIDBERG, S. L., RALL, T. W. & SUTHERLAND, E. W. (1962). *J. biol. Chem.*, **237**, 1239–1243.

LEIMDORFER, A. & METZNER, W. R. (1949). *Am. J. Physiol.*, **157**, 116–121.

MAYNERT, E. W. (1967). *Arch. biol. Med. exp.*, **4**, 36–41.

MUÑOZ, C. (1963). *Acción de las catecolaminas en el sistema nervioso central*, Univ. Chile, Santiago, Chile.

MUÑOZ, C. & PAEILE, C. (1967). *Arch. biol. Med. exp.*, **4**, 63–68.

ROBISON, G. A., BUTCHER, R. W. & SUTHERLAND, E. W. (1967). *Ann. N.Y. Acad. Sci.*, **139**, 703–723.

SIGG, E. B., CAPRIO, G. & SCHNEIDER, J. A. (1958). *Proc. Soc. exp. Biol. Med.*, **97**, 97–100.

SUTHERLAND, E. W. & RALL, T. W. (1960). *Pharmac. Rev.*, **12**, 265–299.

SUTHERLAND, E. W., RALL, T. W. & MENON, T. (1962). *J. biol. Chem.*, **237**, 1220–1227.

WINTER, E. A. & FLATAKER, L. (1950). *J. Pharmac. exp. Ther.*, **98**, 305–317.

WOOLFE, G. & MACDONALD, A. D. (1944). *Ibid.*, **80**, 300–307.