Br. J. Pharmac. (1982), **75**, 485–491

PRODUCTION OF TOLERANCE AND PHYSICAL DEPENDENCE IN THE RAT BY SIMPLE ADMINISTRATION OF MORPHINE IN DRINKING WATER

A.A.-B. BADAWY, C.M. EVANS[1] & M. EVANS

South Glamorgan Health Authority, Addiction Unit Research Laboratory, Whitchurch Hospital, Cardiff CF4 7XB

1 Rats are capable of consuming solutions of morphine sulphate in drinking water *ad libitum* in the absence of taste-masking chemicals and without the need for scheduled provision or prior parenteral administration of the drug.

2 The success of this method depends on the initial provision of a 0.1 mg/ml solution of morphine sulphate.

3 When the drug concentration is increased to 0.4 mg/ml, the rats achieve an average daily intake of 50 mg/kg body wt. each.

4 Daily intake of morphine may be increased by at least about three fold by increasing the drug concentration to 1.2 mg/ml.

5 Oral morphine administration causes only a moderate loss in body weight.

6 Rats whose daily intake of the drug is 50 mg/kg exhibit tolerance to the analgesic action of morphine and show a drastic loss in body weight at 24 h after withdrawal and most of the behavioural symptoms of the naloxone-precipitated withdrawal syndrome.

7 It is suggested that this simple method of morphine administration is suitable for further biochemical and behavioural studies of the actions of the drug.

Introduction

Most investigators of morphine dependence administer the drug parenterally by either repeated injection(s) or implantation of a pellet(s). There are two apparent disadvantages of such procedures, particularly in relation to neurochemical studies. Firstly, these procedures are stressful and may therefore release catecholamines and glucocorticoids, and, thereby, influence biogenic amine metabolism. Secondly, experiments with animals so treated are usually performed many hours after the last of the daily injections of morphine or after removal of the implanted pellets. Under these latter two conditions, the animals could be considered in a state of withdrawal, rather than dependence. We (Badawy, Punjani & Evans, 1981) found that the enhancement of rat brain 5-hydroxytryptamine synthesis caused by chronic morphine administration (in drinking water) is followed rapidly after withdrawal by an inhibition, and suggested that this rapid change (which presumably involves a return of 5-hydroxytryptamine synthesis to normal at some intermediate time-point) may explain the failure of some workers to demonstrate the above chronic morphine-induced enhancement, because of the time lag.

Oral administration of morphine in drinking water may therefore be a better alternative. A major problem encountered by investigators using this method, however, is that of refusal by experimental animals to consume significant amounts of the morphine solution provided, presumably because of its bitter taste (see e.g. Nichols, Headlee & Coppock, 1956; Nichols & Davis, 1959; Kumar, Steinberg & Stolerman, 1969; Stolerman & Kumar, 1970; 1972; Khavari & Risner, 1973; McMillan, Leander, Wilson, Wallace, Fix, Redding & Turk, 1976; Fuentes, Hunt & Crossland, 1978; Gellert & Holtzman, 1978). This aversion and the resultant death of animals reported by some of the above authors have been unfortunately instrumental in hindering the development of this simple method of morphine administration. However, attempts were made to overcome these problems, and these included prior parenteral morphine administration (Kumar *et al.*, 1969), scheduled provision of the drinking solution (Stolerman & Kumar, 1972; Gellert & Holtzman, 1978) and masking the taste of such solution by sucrose (Khavari & Risner, 1973; Fuentes *et al.*, 1978). These manipulations are undesirable for the following reasons: (1) scheduled provision is not representative of morphine intake by human addicts, and is expected to be accompanied by disturbances in electrolyte balance and hormone

[1]Present address: Department of Physiology, The Medical School, University of Birmingham, Birmingham B15.

0007-1188/82/030485-07 $01.00

metabolism that are likely to be caused by the alternate periods of thirst; (2) the effects of sucrose on brain 5-hydroxytryptamine synthesis (Badawy, Punjani & Evans, 1980) resemble those of morphine (Badawy *et al.*, 1981) and may therefore influence their interpretation, particularly in relation to tolerance, dependence and preference. Indeed, Khavari & Risner (1973) reported that sucrose enhances preference to morphine by rats.

One possible explanation of the refusal of experimental animals to drink morphine solutions in the absence of the above manipulations is that, in most of the above studies, the starting concentration of the drug in drinking water was at least 0.3 mg/ml, but not lower. In the only study in which a 0.1 mg/ml solution of morphine was provided (Gellert & Holtzman, 1978), intake was achieved by training the rats from the start to consume their drinking fluids at certain times of the day. These latter authors therefore did not find out if their rats could have accepted the 0.1 mg/ml solution of morphine *ad libitum* without scheduled provision. That rats will do so has been known to us for some time (Badawy & Evans, 1975). We then found that the animals continue to accept the drinking fluid, even when the concentration of morphine sulphate is increased to 0.4 mg/ml. Under these conditions, morphine intake averaged about 50 mg/kg daily and the animals exhibited profound biochemical changes in liver and brain tryptophan metabolism (Badawy & Evans, 1975; Badawy *et al.*, 1981).

We have never attempted to raise the drug intake above, or to find out if rats exhibit tolerance and dependence at, this pharmacologically moderate level of chronic morphine intake. A positive answer to these questions is clearly important, because it is highly desirable to produce the above two major pharmacological effects of morphine by simple administration in drinking water and, thereby, avoid the disadvantages, complications and manipulations described above. In the present paper, we show that the success of this method depends on the initial provision of a very weak solution of the drug (0.1 mg/ml) and that daily intake of a 50 mg/kg body wt. dose (which could, if necessary, be increased by about three fold) is associated with tolerance and physical dependence. A preliminary account of parts of this work has been presented to the British Pharmacological Society (Badawy & Evans, 1981).

Methods

Animals

Male Wistar rats (120 or 150 g ± 4% at the start of experiments) were locally bred. The animals were housed three per cage at a constant temperature (22 ± 1°C) under a natural dark-light cycle and were maintained on cube diet 41B (Oxoid, Basingstoke, Hants.) and water.

Morphine administration and withdrawal

Morphine sulphate was chronically administered in drinking water *ad libitum* to achieve two levels of daily intake, 50 mg/kg body wt. and above.

For both purposes, the drug was provided in increasing concentrations (48 h apart) of 0.1, 0.15, 0.2, 0.3 and finally 0.4 mg/ml. For low morphine intake, the animals continued to receive the latter concentration until the end of the 3-week experimental period. To achieve higher levels of intake, the rats that had already received the above increasing concentrations of the drug for 10 days continued to receive, after the tenth day, solutions (48 h apart) containing concentrations of morphine sulphate of 0.5, 0.6, 0.8, 1.0 and finally 1.2 mg/ml. Body weight was determined in all rats, whereas fluid intake was estimated for each animal from average consumption by the three rats present in each cage. No corrections were made for possible spillage of water or morphine solutions. Morphine withdrawal was achieved by replacing the drug solution with drinking water.

All behavioural studies were performed with rats given the low doses of the drug (those up to 0.4 mg/ml).

In separate experiments performed for short periods of time, groups of rats (9 each) were provided with either drinking water or solutions containing morphine sulphate in concentrations of 0.1, 0.3, 0.5 or 1 mg/ml. Body weight and fluid intake were recorded as described above.

Morphine tolerance

The tail-immersion test was used for this purpose. Groups (5 each) of control and chronically morphine-treated rats received an intraperitoneal injection of either morphine sulphate (2–8 mg/kg body wt.) or an equal volume (2 ml/kg) of 0.9% w/v NaCl solution (saline) between 10 h 00 min and 12 h 00 min, and were tested 20 min later by immersing their tails in water kept at a constant temperature of 55°C. The time (in s) elapsing between immersion and flicking of tails was then recorded.

Morphine withdrawal

The naloxone-precipitated withdrawal syndrome was assessed by the method of Collier, Francis, Henderson & Schneider (1974) after administration of a 1 mg/kg body wt. dose of naloxone hydrochloride to chronically morphine-treated rats. For comparative

purposes, naloxone was administered to control rats, and an equal volume (2.5 ml/kg body wt.) of saline was also injected into both control and chronically morphine-treated animals. The following behavioural parameters were assessed: jumping (from a container, not a platform), wet-dog shakes, diarrhoea, teeth chattering, chewing, paw tremor, writhing, ptosis, head shakes and irritability to both touch and handling.

In addition, the loss in body weight at 24 h after morphine withdrawal was recorded, as was that associated with diarrhoea at 20 min after naloxone administration to chronically morphine-treated rats.

Statistical analysis of results

Most results were analysed statistically by use of Student's *t* test. The morphine withdrawal symptoms precipitated by naloxone (except the faeces weight and the accompanying loss in body weight) were analysed by the chi-squared method and, additionally in certain groups of rats, by the Fisher exact probability test (Siegle, 1956).

Chemicals

Morphine sulphate and naloxone hydrochloride were purchased from Macarthys Ltd (Trecenydd Industrial Estate, Caerphilly, Mid Glam.) and Winthrop Laboratories (Surbiton-upon-Thames, Surrey) respectively. The latter drug was in ampoules, each containing 0.4 mg/ml.

Results

Morphine intake in drinking water

In the initial experiments summarized by Badawy & Evans (1981) in which morphine sulphate was administered in drinking water as originally described by Badawy & Evans (1975), it was found that, although both control and test rats exhibited a steady increase in the intake of water and solutions of morphine sulphate (up to 0.4 mg/ml) respectively over a 3-week period, intake of the latter solutions was consistently, but moderately, lower than that of water. Thus the average daily fluid intake per rat (in ml, means ± s.e. for each group of 20 rats) at the start (day 1) and end (day 21) of the experiment was as follows: control rats (29 ± 1.5 and 40 ± 1 respectively); test rats (25 ± 0.5 and 34 ± 1 respectively). This lag in morphine intake by test rats was not due to the provision of increasing concentrations of the drug, because it was apparent as early as 1 day after the start of the experiment.

The above observations are confirmed by the results illustrated in Figure 1, which also show that, in general, there were no significant differences in fluid intake between rats given the 0.4 mg/ml solution of

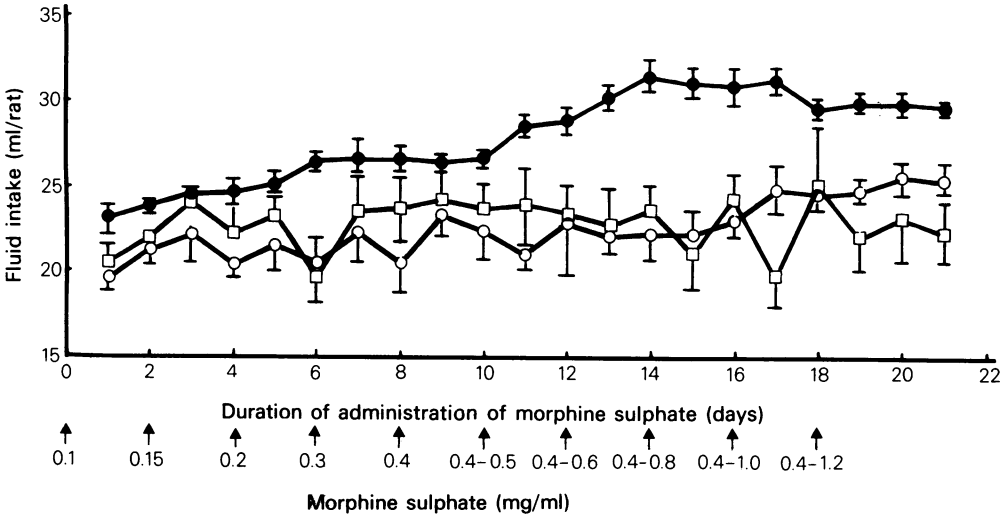

Figure 1 Fluid intake by control and morphine-treated rats. Control rats received drinking water, whereas morphine-treated animals received increasing concentrations of the drug of up to 0.4 mg/ml for the first 10 days. Thereafter some test rats continued to receive the above solution (0.4 mg/ml), whereas others received stronger solutions (of up to 1.2 mg/ml). Values are means for each group of six cages, with each cage containing 3 rats; vertical lines show s.e. Symbols: (●) water intake; (○) low-morphine intake (up to 0.4 mg/ml); (□) high-morphine intake (up to 1.2 mg/ml).

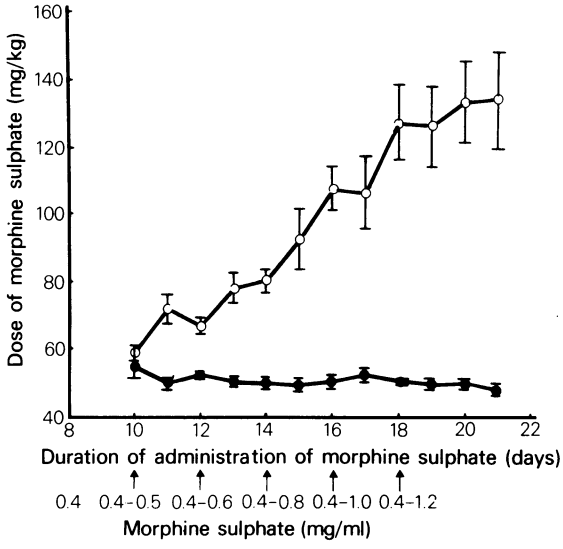

Figure 2 Morphine intake by rats in drinking water. The values shown are derived from fluid intake by the two groups of morphine-treated rats used in the experiments in Figure 1, and are therefore means ± s.e. for each group of 6 cages. Symbols: (●) low-morphine intake; (○) high-morphine intake.

morphine sulphate and those provided with stronger solutions. Fluid intake by both test groups, however, differed significantly ($P < 0.05$ at least) from that of water by control rats, with only one single exception on day 3.

Morphine intake by the above two groups of test rats is shown in Figure 2. Whereas the average daily intake of the 0.4 mg/ml solution (from day 10 onwards) was 50.7 mg/kg (the lowest and highest values were 48.1 and 54.7 respectively), the rats given increasing concentrations of the drug (up to 1.2 mg/ml) showed a steady increase in daily drug intake, which reached a value of 134 mg/kg on the final (twenty-first) day of the experiment.

Acceptability to rats of morphine solutions of various strengths

Because the original (Badawy & Evans, 1975) success of the present method of morphine administration was achieved arbitrarily only through our desire to obtain a moderate level of chronic daily intake of the drug (about 50 mg/kg), it was considered important to find out whether this could be attributed to the possibility that rats accept morphine in drinking water only by the initial provision of a very weak solution. Groups of rats (9 each, 3 per cage) were therefore allowed free access (for 3 days) to a solution containing morphine sulphate in a concentration of 0.1, 0.3, 0.5 or 1 mg/ml. Average intake of the 0.1 mg/ml solution by test rats was 80–83% of that of water by control animals. Intake of the 0.3 mg/ml solution of morphine sulphate was, however, only 45% of control water intake after 1 day, and was increased to up to 70% after the third day. By contrast, intake of the 1 mg/ml solution of the drug was much lower (12–20% of control water intake), whereas that of the 0.5 mg/ml solution occupied an intermediate position. It was also found that, whereas all rats given the 0.1 or 0.3 mg/ml solution of the drug consumed similar volumes, only a third of the animals given stronger solutions of the drug were competent drinkers. These results therefore suggest that morphine intake in drinking water is inversely related to the drug concentration.

Effects of morphine on body weight of rats

In a typical 3-week experiment whose results concerning fluid intake were described at the beginning of this section, the starting and final body weights (in g, means ± s.e. for each group of 20 rats) were as follows: control rats (146 ± 1 and 275 ± 1 respectively); test rats given morphine sulphate in concentrations of up to 0.4 mg/ml of drinking water (153 ± 1 and 261 ± 1 respectively). The latter rats therefore gained weight, but at a rate 19% lower than that achieved by controls. It was also found that this lag in body weight gain by test rats did not start until after the eleventh day of the experiment.

Assessment of body weight in rats given morphine sulphate in concentrations higher than 0.4 mg/ml (see Figure 1 for data on fluid intake) showed that these rats gained weight at a rate not significantly different ($P > 0.10$) from that achieved by the animals maintained on the 0.4 mg/ml solution of the drug. Thus the starting (day 0) and final (day 21) body weights (in g, means ± s.e. for each group of 18 rats) were as follows: control rats (118.8 ± 4.3 and 229.8 ± 4.9 respectively); test rats maintained on the low morphine concentrations (up to 0.4 mg/ml) (121.6 ± 4.1 and 210.3 ± 5.7 respectively); test rats given solutions of the drug of up to 1.2 mg/ml (117.1 ± 5.0 and 199.8 ± 8.7 respectively). The gain in body weight by both groups of morphine-treated rats, however, differed significantly ($P < 0.05$ at least) from that achieved by controls, and, as stated above, this was also evident after the eleventh day.

Morphine tolerance

As shown in Figure 3, tolerance to the analgesic action of acutely administered morphine was observed in rats chronically treated with the drug in drinking water in concentrations of up to 0.4 mg/ml for 3 weeks. The reaction time in the tail-immersion test was significantly ($P = 0.05–0.001$) shortened in

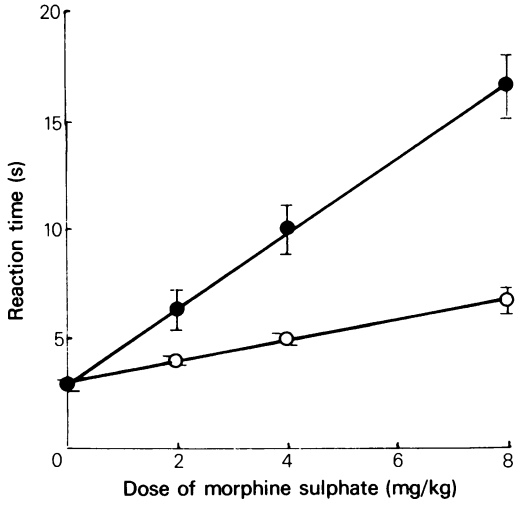

Figure 3 Development of tolerance to the analgesic effect of morphine after its chronic administration in drinking water to rats. Morphine sulphate was administered in drinking water in concentrations of up to 0.4 mg/ml for 3 weeks as in Figure 1. Details of the tail-immersion test are described in the Methods section. Values are means for each group of 5 rats; vertical lines show s.e.mean. Symbols: (●) control rats; (○) chronic morphine-treated rats.

such rats by 36, 51 and 59% after acute administration of doses of the drug of 2, 4 and 8 mg/kg body wt. respectively.

Morphine dependence

Replacement with drinking water of the 0.4 mg/ml solution of morphine sulphate after 3 weeks of provision resulted, 24 h later, in a 24% loss in body weight ($P<0.001$). Thus the starting body wt. (in g, mean ± s.e. for 10 rats) of 175 ± 5 was increased to 300 ± 9 after 3 weeks of morphine intake, but this latter value was decreased to 227 ± 6 at 24 h after withdrawal. Such animals also exhibited an increase in locomotor activity and burrowing in the sawdust, but showed no other signs of spontaneous withdrawal.

Chronically-morphine-treated rats, however, exhibited many of the symptoms of the naloxone-precipitated withdrawal syndrome (Table 1). Thus, of all 11 behavioural parameters tested, only two were either absent (jumping) or did not appear significantly (head shakes).

The results summarized in Table 2 show that, compared with appropriate control rats, the chronically-morphine-treated animals showed significantly more withdrawal symptoms and excreted significantly more faeces and lost more weight during the 20 min following naloxone administration.

Discussion

The present results clearly establish that rats are capable of accepting morphine in drinking water in the absence of taste-masking chemicals and without

Table 1 Naloxone-precipitated withdrawal symptoms in rats chronically treated with morphine in drinking water

	Treatment	*Naloxone*		*Saline*	
	Pretreatment	*Morphine*	*Control*	*Morphine*	*Control*
Test					
Jumping	00/21 (00%)	00/21 (00%)		00/11 (00%)	00/11 (00%)
Wet-dog shakes	11/21 (52%)**	02/21 (10%)		01/11 (09%)	00/11 (00%)
Diarrhoea	20/21 (95%)***	00/21 (00%)		00/11 (00%)	00/11 (00%)
Teeth chattering	14/21 (67%)***	01/21 (05%)		00/11 (00%)	00/11 (00%)
Chewing	12/21 (57%)***	01/21 (05%)		00/11 (00%)	01/11 (09%)
Paw tremor	14/21 (67%)*	05/21 (24%)		01/11 (09%)	01/11 (09%)
Writhing	14/21 (67%)***	00/21 (00%)		00/21 (00%)	00/21 (00%)
Ptosis	12/21 (57%)***	00/21 (00%)		01/11 (09%)	00/11 (00%)
Head shakes	09/21 (43%)	11/21 (52%)		03/11 (27%)	05/11 (45%)
Irritability to:					
touch	09/21 (43%)***	01/21 (05%)		00/11 (00%)	01/11 (09%)
handling	17/21 (81%)***	02/21 (09%)		02/11 (18%)	02/11 (18%)

Morphine sulphate was administered for 3 weeks in drinking water in concentrations not exceeding 0.4 mg/ml as described in the Methods section. Both control and morphine-treated rats received an intraperitoneal injection of either naloxone hydrochloride (1 mg/kg) or an equal volume (2.5 ml/kg) of saline. The differences between control and morphine-treated rats after naloxone administration were analysed by the chi-squared test and are indicated as follows: *$P<0.02$; **$P<0.01$; ***$P<0.001$. There were no significant differences between the three control groups to the right of the Table (Fisher exact probability test). Values given (except percentages) refer to the number of animals responding over the total number used.

Table 2 Summary of the naloxone-precipitated withdrawal symptoms in rats chronically treated with morphine in drinking water

		Injection Naloxone		*Saline*	
	Pretreatment	*Morphine*	*Control*	*Morphine*	*Control*
Test					
Number of withdrawal symptoms		6.3 ± 0.53*	1.1 ± 0.25	0.7 ± 0.26	0.9 ± 0.35
Faeces wt. at 20 min after injection (g)		9.3 ± 0.53*	1.8 ± 0.26	1.1 ± 0.26	1.5 ± 0.33
% loss in body wt. at 20 min after injection		3.3 ± 0.15*	0.6 ± 0.09	0.4 ± 0.10	0.6 ± 0.13

Experimental details, numbers of animals in each group and comparisons of results are as described in Table 1. The number of withdrawal symptoms measured was 11. The differences between control and morphine-treated rats after injection of naloxone were significant at the $^*P < 0.001$ level.

the need for either scheduled provision or prior parenteral administration of the drug. As the results described in the text suggest, the success of this simple method appears to be due to the initial provision of a 0.1 mg/ml solution of the drug. Also, because drug intake is inversely related to drug concentration in drinking water, it may be concluded that the above low concentration not only is acceptable to rats, but also enables them to overcome the aversion to the taste of morphine. Our rats should not be considered atypical in relation to oral morphine intake, because, although many workers (see the introduction) have experienced problems in similar studies, no attempt has previously been made to administer the drug by the initial provision of a 0.1 mg/ml solution in the absence of procedural manipulations. Furthermore, the refusal of our rats to consume significant amounts of solutions of the drug of 0.5–1 mg/ml is in agreement with previously published data (Khavari & Risner, 1973; McMillan *et al.*, 1976; Fuentes *et al.*, 1978). We therefore suggest that our method should enable workers to administer morphine successfully in the drinking water of their own experimental animals, and that, in view of the response of our rats to many of the biochemical and neurochemical effects of the drug, this method is suitable for further studies on morphine dependence.

Our rats receiving a daily dose of morphine sulphate of 50 mg/kg body wt. exhibited tolerance to the analgesic action of the acutely administered drug (Figure 3). Although such tolerance has previously been demonstrated after chronic administration of similar or even-smaller doses by the intraperitoneal route (see e.g. Fernandes, Kluwe & Coper, 1977), our finding nevertheless suggests that the same end result can be achieved by morphine administration in drinking water. This method also leads to the development of physical dependence on morphine, as is suggested by the drastic loss in body weight at 24 h after withdrawal (see the text) and by the significant appearance of 82% of the withdrawal symptoms elicited by naloxone administration (Tables 1–2). The absence of withdrawal jumping in our naloxone-treated morphine-dependent rats may be explained either by the development of tolerance to this effect (which was examined after 3 weeks of chronic morphine administration) or by the fact that the daily dose of the drug (50 mg/kg) was smaller than that usually administered by other workers. This latter possibility appears more likely, because we could not demonstrate the above jumping behaviour after naloxone administration during the first 12 days of oral morphine administration (A.A.-B. Badawy & A. Dacey, unpublished work). We have not examined the jumping behaviour nor any other behavioural parameters in rats given morphine in concentrations larger than 0.4 mg/ml of drinking water, and it therefore remains to be seen whether there are any dose-related differences.

We thank the Medical Council on Alcoholism for the grant of a postdoctoral research fellowship (to C.M.E.) and Mr A. Dacey for animal maintenance. Reprint requests to A.A.-B.B., please.

References

BADAWY, A.A.-B. & EVANS, M. (1975). The effects of ethanol on tryptophan pyrrolase activity and their comparison with those of phenobarbitone and morphine. *Adv. exp. Med. Biol.*, **59**, 229–251.

BADAWY, A.A.-B. & EVANS, C.M. (1981). Naloxone-precipitated withdrawal symptoms in rats chronically treated with small concentrations of morphine in drinking water. *Br. J. Pharmac.*, **74**, 282*P*.

BADAWY, A.A.-B., PUNJANI, N.F. & EVANS, M. (1980). Unsuitability of control sucrose or glucose in studies of the effects of chronic ethanol administration on brain 5-hydroxytryptamine metabolism. *J. Pharmacol. Methods*, **3**, 167–171.

BADAWY, A.A.-B., PUNJANI, N.F. & EVANS, M. (1981). The role of liver tryptophan pyrrolase in the opposite effects of chronic administration and subsequent withdrawal of drugs of dependence on rat brain tryptophan metabolism. *Biochem. J.*, **196**, 161–170.

COLLIER, H.O.J., FRANCIS, D.L., HENDERSON, G. & SCHNEIDER, C. (1974). Quasi morphine-abstinence syndrome. *Nature, Lond.*, **249**, 471–473.

FERNANDES, M., KLUWE, S. & COPER, H. (1977). Quantitative assessment of tolerance to and dependence on morphine in mice. *Naunyn-Schmiedebergs Arch. Pharmac.*, **297**, 53–60.

FUENTES, V.O., HUNT, W.B. & CROSSLAND, J. (1978). The production of morphine tolerance and physical dependence by the oral route in the rat. *Psychopharmac.*, **59**, 65–69.

GELLERT, V.F. & HOLTZMAN, S.G. (1978). Development and maintenance of morphine tolerance and dependence in the rat by scheduled access to morphine drinking solutions. *J. Pharmac. exp. Ther.*, **205**, 536–546.

[illegible]VARI, K.A. & RISNER, M.E. (1973). Opiate dependence produced by ad libitum drinking of morphine in water, saline and sucrose vehicles. *Psychopharmac.*, **30**, 291–302.

KUMAR, R., STEINBERG, H. & STOLERMAN, I.P. (1969). How rats can become dependent on morphine in the course of relieving another need. In *Scientific Basis of Drug Dependence*. ed. Steinberg, H. pp. 209–220. London: Churchill.

McMILLAN, D.E., LEANDER, J.D., WILSON, T.W., WALLACE, S.C., FIX, T., REDDING, S. & TURK, R.T. (1976). Oral ingestion of narcotic analgesics by rats. *J. Pharmac. exp. Ther.*, **196**, 269–279.

NICHOLS, J.R. & DAVIS, W.M. (1969). Drug addiction II. Variation of addiction. *J. Am. Pharm. Assoc.*, **48**, 259–262.

NICHOLS, J.R., HEADLEE, C.P. & COPPOCK, H.W. (1956). Drug addiction I. Addiction by escape training. *J. Am. Pharm. Assoc.*, **45**, 788–791.

SIEGLE, S. (1956). In *Nonparametric Statistics for the Behavioural Sciences*. Tokyo: McGraw-Hill Kogakusha.

STOLERMAN, I.P. & KUMAR, R. (1970). Preferences for morphine in rats: validation of an experimental model of dependence. *Psychopharmac.*, **17**, 137–150.

STOLERMAN, I.P. & KUMAR, R. (1972). Regulation of drug and water intake in rats dependent on morphine. *Psychopharmac.*, **26**, 19–28.

(Received July 22, 1981.
Revised October 19, 1981.)