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Morphine-induced modification of quinine palatability: Effects of multiple morphine-quinine trials

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MORPHINE-INDUCED MODIFICATION OF QUININE PALATABILITY: EFFECTS OF MULTIPLE MORPHINE-QUININE TRIALS

By

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Abstract

Contemporary research investigating the effects of opiate receptor agonists and antagonists indicates a role for endorphinergic mechanisms in the control of consummatory behaviours. One way in which opiates may exert an effect on feeding is by altering the hedonic properties or palatability of food and drink. Investigations of the role of palatability in the effect of opiates on feeding and drinking have primarily considered the effect of single exposures to opiates. Recognizing that chronic exposure to opiates may result in the development of tolerance to their palatability-altering properties, the taste reactivity test, a direct measure of the hedonic properties of a tastant, was used to assess the ability of morphine to modify the palatability of a bitter quinine solution across eight conditioning trials (Experiment 1). Morphine consistently reduced aversive reactions to the quinine solution across all eight conditioning trials, but tolerance did not develop to this effect. In tests for conditioned modification of quinine palatability, administered after the third and the eighth conditioning trial, quinine elicited conditioned attenuation of aversive reactions in the Contingent, but not in the Noncontingent group. Hence, there was evidence of drug-similar conditioned responses suggesting that an association had been established between the effect of morphine on palatability, and the taste of quinine. In order to determine how rapidly this association was established, a second experiment was conducted whereby subjects received a single injection of morphine 30 min prior to a 10 min infusion of quinine. The results of this experiment indicated that a single exposure

is insufficient for the formation of an association between the effect of morphine on palatability, and the taste of quinine. In summary, therefore, tolerance did not develop to the ability of morphine to attenuate aversive reactions to the taste of quinine. Furthermore, quinine elicited conditioned attenuation of aversive reactions when assessed during drug-free tests, suggesting that the palatability of quinine was conditionally altered in a positive direction following its association with morphine.

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Introduction

Over the past 20 years, research has indicated that the endogenous opioid system plays an important role in the regulation of eating and drinking. At naturally occurring concentrations, opiate antagonists, for example, naloxone and naltrexone, inhibit ingestive behaviours in both deprived and nondeprived animals (Brown & Holtzman, 1979, 1981; Czech & Stein, 1980; Le Magnen, Marfaing-Jallat, Miceli & Devos, 1980). Conversely, opiate agonists, for example morphine, at appropriate dose levels, enhance ingestive behaviours (Calcagnetti & Reid, 1983; Cooper, 1981; Gosnell & Majchrzak, 1989; Jalowiec, Panksepp, Zolovick, Najam, Herman, 1981; Maickel, Braude & Zabik, 1977; Milano, Wild, Hui, Hubbell & Reid, 1989). The mechanisms responsible for this opiate regulation of feeding are currently the focus of research investigations. One putative mechanism that is receiving considerable attention is that of opiate-induced modification of palatability. According to the palatability hypothesis, opiate-induced changes in the palatability of tastants precipitate opiate-induced effects on ingestion. Notably, contemporary research on the role of palatability in opiate-induced changes in ingestion has primarily considered the effect of acute or single exposures to opiates. It is conceivable, however, that chronic exposure to opiates may result in the development of tolerance to their effects on palatability, and ultimately, ingestion. The present study will review some of the research to date on opiates and feeding. This review will provide the rationale for two experiments designed to determine whether tolerance develops to morphine-induced changes in the palatability of quinine.

Effects of Opiate Antagonists and Agonists on Chow and Water Consumption

Holtzman (1974) provided the earliest evidence that opiate antagonists exert an inhibitory effect on ingestive behaviour, with the report that the opiate antagonist naloxone blocked the normal intake of food in rats that had been food-deprived for 48 hours. In a follow-up study, Holtzman (1975) also observed an inhibitory effect of naloxone on the intake of a sweetened milk solution. Subsequently, Brown and Holtzman (1979) determined that naloxone also inhibited water consumption regardless of the sex of the animals, the extent to which they had been water-deprived, and the time of day of the test. Low doses of naloxone (0.1 - 1.0 mg/kg) significantly decreased water consumption by 30% to 50%. Collectively, these findings suggest that naloxone exerts a nonspecific inhibitory effect on ingestive behaviour regardless of the taste of the solution.

There is also evidence that motivational factors modify the suppression of feeding produced by naloxone. Brown and Holtzman (1979) reported that the strength of the naloxone-induced inhibition of food consumption varied according to food-deprivation conditions. A low dose of naloxone (1 mg/kg) reduced food consumption by 40% in rats that had been food-deprived for 24 hours. As the period of deprivation increased, however, the suppressant effects of naloxone decreased. Thus, only a high dose of naloxone (10 mg/kg) inhibited feeding in animals that had been food-deprived for 45 hours. A similar effect was observed for water consumption under different levels of food-deprivation. Therefore, motivational factors may influence the display of naloxone-induced suppression of

food intake.

Not only has naloxone been shown to inhibit food intake (Brown & Holtzman, 1979), but naltrexone, a longer-acting opiate antagonist, has also been shown to produce a suppressant effect on ingestive behaviours. Grandison and Guidotti (1977) reported that intraperitoneal (ip) injections of naltrexone (3.1 μmole/kg) blocked eating induced by intrahypothalamic injections of beta-endorphin, an endogenous opiate receptor agonist which is considered to be involved in the regulation of feeding.

The inhibitory effects of naloxone and naltrexone on water intake have also been demonstrated in rats which exhibit deficiencies in various opiate-mediated functions. Brown and Holtzman (1981) reported that both opiate antagonists, at doses ranging from 0.01 to 10 mg/kg, suppressed water consumption induced by deprivation in homo- and hetero-zygous Brattleboro rats. This strain of rats manifests severe hypothalamic *diabetes insipidus* due to a deficiency in the synthesis of vasopressin, a peptide hormone involved in water metabolism. Furthermore, these rats exhibit excessive water intake, and display impairments in various opiate-mediated functions (e.g., they fail to develop tolerance to the analgesic effects of opiates). Brown and Holtzman (1981) demonstrated, however, that Brattleboro rats, like normals, display a dose-dependent naloxone- and naltrexone-induced suppression of water consumption. Nevertheless, consistent with previous research, there were differences in the effects of naloxone and naltrexone. Longer-acting naltrexone maximally reduced water-intake by 90%,

whereas shorter-acting naloxone decreased water-intake by 55%. Furthermore, the suppressant effects of naltrexone were still evident up to 3.5 hours following administration. Thus, naltrexone appears to be more potent than naloxone in suppressing water intake. Moreover, the abnormalities in the opiate and vasopressin systems of the Brattleboro rats did not appear to modify the suppressant effect of naltrexone and naloxone on water consumption.

While there is convincing evidence that opiate antagonists suppress ingestive responses, the extent to which opiate agonists stimulate consummatory behaviours is more controversial. Whereas some researchers have identified a stimulatory effect of opiate agonists on consumption (e.g., Calcagnetti & Reid, 1983; Cooper, 1981; Evans & Vaccarino, 1990; Grandison & Guidotti, 1977; Milano et al., 1989); others report a dose-dependent biphasic effect (e.g., Gosnell & Majchrzak, 1989; Jalowiec et al., 1981; Maickel et al., 1977; Touzani, Akarid & Velley, 1991); and the remainder report a suppressant effect of opiate agonists on consumption (e.g., Spencer et al., 1986).

One of the earliest studies to report a stimulatory effect of opiate agonists on food consumption was conducted by Grandison and Guidotti (1977). Male, Sprague-Dawley rats were first implanted with cannulae in the ventromedial hypothalamus. After recovery, satiated rats were given intrahypothalamic injections of beta-endorphin (1.46 nmoles), an endogenous opioid peptide, and were then placed in individual cages with a weighed pellet of Purina rat chow. Thirty minutes after the injection, the pellet along with loose food particles was

reweighed. According to the researchers, beta-endorphin precipitated an increase in feeding which was subsequently suppressed by an injection of naltrexone (3.1 μmole/kg, ip).

Maickel et al. (1977) extended research on opiate-induced regulation of consummatory behaviour by considering the effects of a variety of opiate agonists and antagonists on the water intake of fluid-deprived rats. These researchers reported that several opiate antagonists suppressed water intake, while several opiate agonists produced a biphasic effect, that is, an initial suppression of consumption followed by an enhancement of consumption. First, baseline levels of water intake were assessed one week prior to the testing of drug effects. During testing water intake was measured every 15, 30 and 60 min. The antagonists, levallorphan, naltrexone and naloxone, along with the mixed agonist-antagonist cyclazocine, all produced dose-dependent reductions in fluid-intake, with cyclazocine being the most potent and naloxone the least potent. The agonists, methadone, morphine, opium alkaloids, pentazocine and meperidine all produced biphasic effects. Low doses of these agonists enhanced water intake; however, as dosages increased, there was a concurrent decrease in water intake. In terms of potency, methadone was the most effective compound and meperidine the least.

The biphasic effect of opiate agonists on water intake reported by Maickel et al. (1977), however, may have been mediated by the length of the test session used in their study. Theoretically, according to Milano et al. (1989), the enhancing effect of opiate agonists is dependent upon a critical blood concentration

of the opiate; when the concentration is too high, the effect is suppressed consumption. With time, however, as the drug is metabolized, and the blood concentration decreases, the effect is enhanced consumption. Thus, when administering high doses of opiate agonists, long test sessions (> 1 hr) are mandatory in order to observe the enhancing effect of opiate agonists on fluid intake, since time is needed to reduce the blood concentration of the agonists. Therefore, it is conceivable that in the study conducted by Maickel et al. (1977), the test sessions (60 min maximum) were not long enough to manifest the enhancing effects of high doses of opiate agonists. Consequently, their observations may not be representative of the true effect of opiate agonists on ingestive behaviour. This analysis was confirmed by an experiment conducted by Jalowiec et al. (1981). These authors reported a partial biphasic effect of morphine on food and water intake. They observed a reliable increase in food and water intake following pretreatment with one of three different doses of morphine, 1.0, 2.5 and 5.0 mg/kg, during a 4 hour test session. At one hour into the test session, however, morphine did not affect food intake but did reliably reduce water intake. Four hours after the injection, however, both food and water intake were reliably increased by 50-75% and 90-130% respectively.

As evident from the research which has been reviewed, there is convincing support for the contention that opiate agonists and antagonists exert a stimulatory or suppressant effect on consummatory behaviours. Contemporary empirical research suggests that the effect of opiates on feeding is moderated by several

factors including, the dose administered, deprivation conditions and the length of the test period. While factors which moderate the effect of opiates on consummatory behaviour have been identified, the mechanisms which are responsible for this phenomenon have yet to be fully delineated.

Hypotheses to Account for the Effects of Opiates on Ingestive Behaviour: Palatability Shift or Post-Ingestive Feedback Mechanisms?

Since the initial demonstration that opiates modify ingestion, several hypotheses have been generated to account for this phenomenon (for reviews see Cooper, Jackson, Kirkham & Turkish, 1988; Sanger, 1983). Among the explanations advanced is the possibility that the increase or decrease in food intake, produced by opiate agonists and antagonists, is nonspecific, and reflects changes in general activity. There is evidence, however, of a dissociation between the effects of opiates on general activity, and their effects on ingestion. For example, ethylketocyclazocine, a *kappa* agonist which causes a decrease in general activity, still produces an increase in ingestion (Sanger & McCarthy, 1981). Furthermore, Carey, Ross and Enns (1981) reported that while naloxone reduced the food and water intake of rats housed in running wheels, it did not significantly affect the number of wheel revolutions made by these animals. Hence, the "activity" hypothesis does not adequately account for the effect of opiates on ingestion.

Belluzzi and Stein (1977) proposed that the effect of opiates on feeding

may be due to the action of opiates on the physiological system mediating reward. These authors argued that opiates mediate the drive-reducing aspect of reward which results in a "state of satisfaction following the attainment or consumption of a goal." Thus, the reward value of food may be increased or decreased by opiate agonists and antagonists respectively, resulting in an increase or decrease in food intake. Based on this conceptualization, however, it follows that the administration of opiate agonists should produce gradual satiation or a reduction in the consumption of reward. As evident by the reported research, however, and as conceded by Belluzzi and Stein (1977), this is clearly not the case since opiate agonists produce an increase in consumption. Therefore, the "drive-reduction" hypothesis does not adequately account for the effect of opiates on feeding.

Post-ingestive factors have also been thought to play a role in the effect of opiates on feeding. It has been suggested that opiates alter the net holding capacity of the gut, resulting in an increase or decrease in consumption. It has also been suggested that opiate antagonists may interfere with the normal metabolism of sugars, thus suppressing intake by enhancing negative feedback from the periphery. According to one school of thought, opiate antagonists enhance satiety, thus causing a decrease in food intake, while opiate agonists increase food consumption by opposing satiety (Cooper, 1981; Kirkham & Blundell, 1984, 1986). In contrast, other research suggests that the effect of opiates on feeding is not mediated by post-ingestive factors but by pre-ingestive factors, specifically palatability. According to this hypothesis, opiate antagonists decrease the

palatability of tastants resulting in a decrease in food intake, while opiate agonists increase the palatability of tastants producing an increase in food intake.

Notably, the palatability hypothesis seems similar to the drive-reduction hypothesis proposed by Belluzzi and Stein (1977). Theoretically, if palatability represents an indication of the reward value of food then, according to Belluzzi and Stein (1977), it is conceivable that opiate agonists and antagonists will cause an increase or decrease in the palatability of food, and ultimately consumption. Belluzzi and Stein (1977) contend, however, that opiates mediate the drive-reducing aspects of reward such that, over time, there should be evidence of satiety or a gradual reduction in the consumption of reward. The palatability hypothesis makes no such assumption, and therein lies the difference between these two hypotheses. Therefore, for example, while Belluzzi and Stein (1977) would predict that any increase in the palatability and consumption of food caused by an opiate agonist would eventually peak, the palatability hypothesis suggests that there should be a consistent effect of the agonist on palatability and consumption.

Two procedures are employed in the literature to assess the relative contribution of post-ingestive factors and palatability to opioid-induced modifications of feeding. The first procedure involves the use of choice tests between saccharin-flavoured food or water, and plain food or water. Since saccharin does not contain nutrients, it does not produce post-ingestive consequences beyond those produced by plain water or food. Any selective

modification in preference for saccharin is thus attributed to a modification in palatability, rather than to a modification in post-ingestive consequences. The second procedure is that of sham-feeding or drinking. In this procedure, animals are surgically prepared with a gastric fistula. When the fistula is open, any food that enters the stomach of the animal is immediately removed, presenting no post-ingestive consequences of feeding. The opiate-induced modification of feeding in animals with open gastric fistulae is thus interpreted as a modification of the oral factors (predominantly palatability) that contribute to feeding, rather than a modification of post-ingestive consequences. The experiments reported below are arranged into those which employ one or the other of these techniques.

Using the sham-drinking procedure, Rockwood, Siviy and Reid (1981) determined that the effect of naloxone on consumption is not mediated by post-ingestive factors. They investigated the ability of naloxone to modify water intake of sham-drinking rats with open gastric fistulae. These authors reported that naloxone, at doses of 1.0 and 10.0 mg/kg, reliably reduced sham-drinking in water-deprived rats. These results suggest that naloxone-induced suppression of drinking is mediated by oral factors, rather than peripheral gut-related factors. Since the post-ingestive feedback cues are unavailable in rats that sham-drink, the effects of naloxone on drinking must be mediated by a mechanism other than a gut-related feedback cue. As such, the effect of opiate antagonists on feeding appears to be mediated by oral factors. Notably, this suggestion has been supported by subsequent research (Gosnell & Majchrzak, 1989; Linesman, 1989;

Spencer et al. 1986). In a follow-up study, Rockwood and Reid (1982) investigated the effect of naloxone on the fluid intake and preference of sham-drinking rats given the choice between drinking water or a 10% sucrose solution in a one hour, two-bottle test. Fifteen minutes prior to the choice test, rats received an injection of saline, naloxone (0.5, 1.0, 5.0, 10 mg/kg) or no injection. All of the animals were tested under two deprivation conditions: 22.5 hours of fluid deprivation and no deprivation. Rockwood and Reid (1982), found that naloxone preferentially reduced the sucrose intake of sham-drinking rats, regardless of deprivation condition. This result also suggests that the inhibitory effect of naloxone on intake is mediated by an oral mechanism.

Sham-drinking experiments, therefore, provide evidence that opiate antagonists reduce the palatability of the tastant. This finding is supported by the results of other research which assessed the effects of opiate antagonists on saccharin preference in choice tests. As stated previously, in choice tests the animal is provided with two types of fluid or food; one type is sweetened with non-nutritive saccharin and the other is not sweetened. If a drug selectively modifies the intake of the sweetened food or fluid, then it is presumed that the drug modifies the palatability of that food or fluid.

Le Magnen et al. (1980) reported that naloxone (1 mg/kg) significantly decreased preference for a 0.05% saccharin solution in a two-bottle choice test with water. Siviy, Calcagnetti and Reid (1982) reported a similar finding in a two-bottle choice test between water and one of five saccharin concentrations: .006%,

.05%, .15%, .5% and 1.0% saccharin. Deprived rats were given one of three doses of naloxone (0.1, 1.0 and 5.0 mg/kg) prior to the presentation of the fluids. Naloxone produced a dose-dependent decrease in the preference for saccharin, relative to water, across all of the saccharin concentrations. Naloxone, therefore, modified the palatability of the fluid, thereby reducing consumption. The effects of the opiate agonist morphine on preference for saccharin, however, were not directly parallel. It was reported that a 2 mg/kg dose of morphine caused a three-fold increase in the intake of a 0.5% saccharin solution, while being ineffective in modifying consumption of a lower concentration (0.006%) of saccharin solution. Siviy et al. (1982) noted that the 0.5% concentration of saccharin was less preferred than water in controls, presumably because of its bitter taste. This led these authors to suggest that morphine may be working to reduce the aversive qualities of this concentration, thus increasing preference for it. That is, morphine may not increase the palatability of a sweet taste, but instead suppress the aversive properties of an aversive taste. Such a modification of palatability would also increase consumption.

In further support of the palatability hypothesis, Apfelbaum and Mandenoff (1981) reported a suppressant effect of naltrexone on hyperphagia, induced by the presentation of highly palatable foods. Naltrexone produced a dose-dependent reduction in intake in animals given unrestricted access to highly palatable foods (e.g. cookies, lard, chocolate), but not in animals given unrestricted access to chow. Thus, the inhibitory effect of opiate antagonists on food consumption

appears to be mediated by the same mechanism that controls water intake - the palatability of the tastant.

The role of opiate antagonists as antidipsogenic agents has been observed using a variety of stimuli including sweet-tasting liquids such as sucrose, glucose and saccharin solutions (Cooper, 1983; Jalowiec et al., 1981; Lynch, 1986; Lynch & Burns, 1990; Lynch & Libby, 1983; Parker, Maier, Rennie & Crebolder, 1992; Touzani et al., 1991), salt solutions (Cooper & Turkish, 1981) and alcohol (Linesman, 1989). Several of these studies also provide support for the contention that the inhibitory effect of opiate antagonists on feeding is moderated by changes in the palatability of tastants.

Cooper (1983) investigated the effect of naloxone and naltrexone on preference for non-nutritive saccharin solutions in a two-bottle choice test between saccharin (.01% or .05%) and water. He observed that both antagonists produced dose-dependent reductions in saccharin preference in a 30 min choice test. For the 0.01% saccharin solution, naloxone at dose levels of 0.1 mg/kg - 10 mg/kg, and naltrexone at dose levels of 0.3 mg/kg - 10 mg/kg suppressed saccharin preference. In the choice test between the 0.05% saccharin solution and water, 3 - 10 mg/kg of naloxone and 1 - 10 mg/kg of naltrexone suppressed saccharin preference. Naltrexone (1 - 10 mg/kg) and naloxone (3 and 10 mg/kg) produced significant decreases in the consumption of the saccharin solutions without corresponding reductions in water consumption. Thus, both naloxone and naltrexone selectively modified the preference for a highly palatable solution.

Since a 1 mg/kg dose of naltrexone produced a suppression of saccharin preference, but a dose of 3 mg/kg of naloxone was required, Cooper's (1983) results suggest that the longer acting opiate antagonist naltrexone is more potent as an anorexigenic agent.

Notably, Brown and Holtzman (1979) reported a dose-dependent decrease in water intake following pretreatment with naloxone, which Cooper (1983) did not observe. The primary reason for this discrepancy may be the fact that Cooper (1983) used a choice design in his study such that saccharin and water were both available simultaneously, whereas Brown and Holtzman (1979) tested water intake only, in a single-bottle test. The fact that Cooper (1983) found that both naloxone and naltrexone produced a decrease in the intake of the saccharin solution with minimal effect on water intake would suggest that opiate antagonists preferentially inhibit the intake of palatable substances. Furthermore, Cooper's findings support the argument that the suppressant effects of opiate antagonists on fluids do not require nutritive post-ingestive consequences, but may be mediated by a palatability shift.

Lynch (1986) also used a choice test to ascertain the lowest dose of naloxone sufficient to produce a decrease in saccharin preference, as well as to examine the effect of moderate daily doses of naloxone on saccharin preference. He reported that the suppressant effect of naloxone on the preference for a 0.1% saccharin solution varied in a dose-dependent manner. Specifically, higher doses of naloxone (0.1, 0.3 , 1.0 mg/kg) were more effective than lower doses (0.03

mg/kg) in reducing saccharin preference, with water intake remaining virtually unaffected. Furthermore, Lynch (1986) demonstrated that the effectiveness of naloxone in reducing saccharin preference varied with the saccharin concentration. As the concentration of saccharin increased, the suppressant effect of naloxone decreased. According to Lynch (1986), these observations suggest that fluid intake, motivated by a sweet taste, is extremely sensitive to the disruptive effects of opiate receptor blockade. Furthermore, the results suggest that the effectiveness of naloxone varies with saccharin concentration, such that near the preference threshold, low doses of naloxone are effective in suppressing saccharin consumption, but become less effective above threshold.

Touzani et al. (1991) extended the findings of Lynch (1986) by investigating the interaction between naloxone dose and saccharin concentrations. This was accomplished by analyzing the relationship between several doses of naloxone (0.01, 0.1, 1.0 mg/kg) and preference for different concentrations of saccharin (0.007%, .024%, .04%). As anticipated, the suppressant effect of naloxone on saccharin preference appeared to be based on the dose administered and the concentration of the saccharin solution. The higher doses of naloxone (0.1 and 1.0 mg/kg) decreased saccharin preference at all three concentrations, while causing only a moderate decrease in water consumption. Paradoxically, however, the lowest dose of naloxone (0.01 mg/kg) produced an increase in saccharin consumption at the .024% concentration, with a corresponding decrease in water intake, but a decrease in both saccharin and water intake at the highest

concentration of saccharin (.04%). Therefore, at a low dose, naloxone produced a biphasic effect on saccharin consumption dependent upon the saccharin concentration. According to Touzani et al. (1991), it is conceivable that the enhancing effect of low doses of naloxone on the intake of weaker saccharin concentrations may be due to the preferential stimulation of opiate autoreceptors, thereby suppressing the release of natural opiates; the ability of higher saccharin concentrations to release opiates themselves may override this effect. The suppressant effect of higher doses of naloxone on saccharin consumption may be due to the stimulation of postsynaptic opioid receptors. It is also possible that the different responses are due to dose-dependent differential stimulation of different opioid receptor subtypes.

Lynch and Libby (1983) extended support for the palatability argument by assessing the effects of both opiate antagonists (naloxone) and agonists (morphine) on saccharin consumption. Nondeprived and food-deprived rats were given an injection of saline, naloxone (1 mg/kg) or morphine (0.1 mg/kg), 15 min (30 min for morphine) prior to a two-bottle choice test between water and one of five saccharin solutions (.001, 0.01, 0.1, 1.0, or 10%), for one hour. For the non-deprived animals, naloxone significantly decreased intake of the two most preferred saccharin solutions, 0.1% and 1.0%, with minimal effect on the concentrations above or below these levels. Morphine, on the other hand, enhanced the intake of only the highest concentration of saccharin, an extremely bitter 10% saccharin solution. For the food-deprived rats, naloxone significantly

suppressed intake of all but the highest saccharin concentration. This result, in particular, supports the palatability hypothesis since there was a selective decrease in the intake of the preferred solution rather than a decrement in consumption of all fluids in general. In agreement with the previous report by Siviy et al. (1982), morphine modified preference for only the unpalatable, bitter, 10% saccharin solution. Thus, the fact that morphine increased intake of this aversive concentration, while failing to exert an effect on the more palatable concentrations, indicates that the effect of morphine may have been to reduce the aversive taste properties rather than increase the positive taste properties of saccharin, rendering it more palatable.

On the other hand, Calcagnetti and Reid (1983) reported a stimulatory effect of the opiate agonist morphine on saccharin preference. One group of rats was habituated to a 12 hour water-deprivation schedule, while another group remained nondeprived. On the test day, all of the rats were injected subcutaneously (sc) with either morphine (2 mg/kg) or saline solution, 30 min prior to a one hour presentation of two bottles: one containing water and the other containing one of five saccharin concentrations (0.006, 0.05, 0 15, 0.5 and 1.0%). For both the deprived and nondeprived rats, morphine enhanced the preference for the saccharin solutions, including the highest concentration which was consumed slightly less than water in the saline pretreated group. These results support the contention that the enhancing effect of morphine is moderated by the palatability of tastants. The fact that there was an increase in saccharin consumption without a

parallel increase in water intake would suggest that the effect of morphine is not simply to increase drinking but specifically to increase the intake of palatable tastants.

Morphine has also been reported to enhance sucrose consumption, especially during lengthy test sessions (Milano et al., 1989). Milano et al. (1989) placed rats on a schedule of 22 hours of water-deprivation followed by the simultaneous presentation of water and 20% sucrose solution for two hours. Immediately prior to the presentation of the fluids, morphine was administered subcutaneously at a dose of 1 mg/kg. The results indicated that morphine selectively increased intake of the sucrose solution and decreased intake of water. This finding provides further support for the argument the enhancement of feeding produced by pretreatment with morphine is mediated by the palatability of the substance consumed.

Touzani et al. (1991) extended research on the biphasic effect of morphine on fluid intake by investigating the effect of different doses of morphine on preference for a .007% saccharin solution in a one hour choice test. Thirty minutes before the fluids were presented, rats were injected with one of three doses of morphine: 0.1 mg/kg, 0.5 mg/kg and 1.0 mg/kg, sc. The results indicated that each dose of morphine significantly decreased saccharin preference, and the highest dose (1 mg/kg) was observed to elicit a significant compensatory increase in water consumption. In a second experiment, three groups of rats were injected with a 1 mg/kg dose of morphine, 30 min prior to a one hour saccharin-

water choice test using three different concentrations of saccharin: .007%, .024% and .04%. As in the first experiment, morphine decreased saccharin preference at the .007% concentration. With the two higher concentrations, however, the effect of morphine pretreatment was reversed resulting in an increase in the preference for saccharin. Thus, as has been observed with naloxone (e.g., Lynch, 1986), the stimulatory effects of morphine appear to be moderated by the concentration of the taste stimuli. Therefore, the failure of morphine to enhance preference for the lower concentration of saccharin (.007%) in the first experiment may have been a function of its below threshold concentration. It must be noted, however, that Calcagnetti and Reid (1983) using a higher dose of morphine (2 mg/kg) reported an increase in the intake of a 0.006% saccharin solution.

Research indicates that the effect of opiates on palatability is not receptor-specific (Calcagnetti & Reid, 1983; Cooper, Jackson & Kirkham, 1985; Gosnell & Majchrzak, 1989). There are four types of opiate receptors: *mu*, *delta*, *kappa* and *sigma* (Julien, 1988). The *mu* receptors are localised in the brainstem and medial thalamic areas and appear to mediate opiate-induced analgesia and respiratory depression; *delta* receptors are located in the emotion-modulating centres of the brain (the limbic system) and appear to be involved in affective behaviour and euphoria; *kappa* receptors are located in deep layers of the cerebral cortex and spinal cord, and may mediate sedating analgesia; while *sigma* receptors are located primarily in the limbic system and may mediate the dysphoria and hallucinations that some opiates induce. Empirical research on the role of palatability in opiate-

induced modifications of consummatory behaviour suggests that the *mu*, *delta* and *kappa* receptors may all be involved in this phenomenon.

Gosnell and Majchrzak (1989) reported evidence of an opiate-mediated increase in preference for saccharin following intracerebroventricular (ICV) injections of [D-Ala^2, MePheGly-ol^5]enkephalin (DAGO), a selective *mu* agonist, Tyr-D-Thr-Gly-Phe-Leu-Thr (DTLET), a selective *delta* agonist; and, an opiate-mediated decrease in the preference for saccharin following ICV injections of U50,488H, a selective *kappa* agonist, and naloxone. During testing, animals received injections of DAGO (1 or 3 nmol), DTLET (1 or 3 nmol), U50,488H (30, 100 nmol) or naloxone (83 or 275nmol) prior to a 3 hour choice test between water and saccharin (0.15%). Gosnell and Majchrzak reported that DAGO produced a significant increase in saccharin preference that was dose specific; 3 nmol produced a greater increase than 1 nmol of DAGO. The effect of DTLET paralleled that of DAGO; the 3 nmol dose produced a greater increase in preference for the saccharin solution than the 1 nmol dose. Contrary to expectations, however, the effect of the selective *kappa* agonist U50,488H, paralleled that of naloxone in that it reduced saccharin intake.

The observations made by Gosnell and Majchrzak (1989) are somewhat consistent with reports made by other researchers (e.g., Calcagnetti & Reid, 1983). Based on these observations, they suggest that opiate agonists do stimulate consummatory behaviours. The suppression of saccharin intake contingent on pretreatment with the selective *kappa* agonist U50,488H would suggest, however,

that, as is the case with opiate antagonists, there are certain exceptions. Although Gosnell and Majchrzak (1989) did not observe an increase in preference for saccharin following pretreatment with a *kappa* agonist, other researchers have observed such an increase (see Cooper, Jackson & Kirkham, 1985, for review). Thus, research suggests that *mu*, *delta* and *kappa* opiate agonists can exert stimulatory effects on ingestion.

In an effort to investigate the palatability hypothesis, Evans and Vaccarino (1990) examined the effects of morphine on food choice, and on the intake of foods varying in palatability. They demonstrated that morphine (2 mg/kg) selectively enhanced preference for sucrose or a 10% sucrose-chow mixture, but did not modify preference for unsweetened chow. This finding suggests that the ability of morphine to enhance preference for sweetened food was mediated by palatability rather than post-ingestive factors since a similar effect was observed when chow was sweetened with non-nutritive saccharin (.018%). Moreover, when rats were pretreated with naloxone (.125, .5 or 1.0 mg/kg), the morphine-induced preference for food was blocked.

In an attempt to isolate the central mechanism controlling this phenomenon, Evans and Vaccarino (1990) examined the effect of injections of morphine (1.0, 4.0 and 8.0 μg) to the caudate nucleus and the nucleus accumbens (a critical site for opiate reward), on ingestive behaviour. The nucleus accumbens seems to be involved in the effects of morphine on feeding since injections to this site stimulated palatability-mediated feeding. No such observations were made after

injections to the caudate nucleus. Notably, morphine injected to the nucleus accumbens significantly enhanced intake of sucrose at all doses.

The observations made by Evans and Vaccarino (1990) are consistent with other research. Notably, rats with gastric fistulae who sham-drink still exhibit a decrease in fluid intake following treatment with naloxone (Rockwood, Siviy & Reid, 1981; Rockwood & Reid, 1982). Furthermore, as reported by Siviy et al. (1982), naloxone causes a decrease in the normal preference for saccharin. Hence, a saccharin concentration that is considered pleasant, by humans, under normal circumstances, is perceived as somewhat aversive after treatment with naloxone. In this same study, it was reported that morphine increased the intake of higher concentrations of saccharin but was ineffective at lower concentrations. Since saccharin is non-nutritive, and thus has no direct post-ingestive consequences, this finding also implies that opiates act to alter the palatability of the taste of the solution.

Gosnell, Krahn and Majchrzak (1990) reported that the effect of morphine is moderated by baseline diet preferences. These researchers investigated the effect of morphine (0, 2 and 10 mg/kg, sc) on the intake of carbohydrates, fat and protein. Their results indicated that the effect of morphine on diet selection is positively correlated with pre-existing baseline intakes of carbohydrate, fat and protein. Furthermore, a significant positive correlation was found between daily intake of a given nutrient and the effect of morphine on the intake of that nutrient. This finding is consistent with the observation that morphine causes an increase in

the intake of preferred foods as reported by Evans and Vaccarino (1990).

Support for opioid involvement in the palatability of food has also been found with human subjects. This is exemplified in the work of Yeomans and Wright (1991), who investigated the perceived hedonic properties of food by humans following oral administration of 2.5 mg of nalmefene, an opioid antagonist derived from naltrexone. First, subjects rated various sensory qualities of food from a standard buffet (e.g., tuna, ryvita, tortilla) and were then allowed to eat from the buffet, which consisted of ten items. The nalmefene-treated group gave significantly lower ratings of the attractiveness of the smell, and the taste of certain foods, but not the appearance of any food. Significantly lower attractiveness ratings were seen with gouda and pakora both of which have strong smells. Similarly, only those foods whose tastes were rated as highly attractive by the controls (e.g. ham, pakora, gouda) were significantly lower in rated attractiveness in the nalmefene-treated group. In terms of intake, the nalmefene-treated group ate significantly less of the buffet-style meal, both in terms of weight ingested and caloric intake.

According to Yeomans and Wright (1991) the results of this study are important since they support the hypothesis that endogenous opioids are involved in processes underlying the perception of the attractiveness of foods. This finding is in agreement with that of other researchers. Cooper and Turkish (1989) reported that naltrexone reduced the intake of chocolate cookies, but enhanced intake of laboratory chow in a choice exercise. Apfelbaum and Mandenoff (1981)

reported that naltrexone treatment caused a reduction in the intake of rats eating cafeteria diets (e.g., high fat and carbohydrate) while marginally decreasing the intake of rats eating laboratory chow.

Thus far, there is considerable support for the hypothesis that the effects of opiate antagonists and agonists are mediated by alterations in the palatability of taste stimuli. It has been demonstrated that opiate agonists cause an increase in the intake of preferred foods (Evans & Vaccarino, 1990; Gosnell et al., 1990; Lynch & Burns, 1990, Yeomans & Wright, 1991). There are also reports, however, indicating that opiate agonists only enhance the intake of highly concentrated saccharin solutions by reducing the bitter taste properties that mask the sweet taste properties (Lynch & Libby, 1983; Siviy et al., 1982). In contrast, opiate antagonists consistently decrease the perceived attractiveness and intake of highly preferred foods (Cooper, 1983; Cooper & Gilbert, 1984; Le Magnen et al., 1982; Lynch & Libby, 1983; Siviy et al., 1982), except at extremely low doses that may selectively block autoreceptors allowing a greater release of endogenous opioids (Touzani et al., 1991).

Effects of Chronic Exposure to Opiates on Intake: Does Tolerance develop to Opiate-Induced Modifications of Intake?

The research reviewed above investigated the effect of a single or short term exposure to opiate agonists or antagonists on feeding. A number of investigators have also examined the effect of chronic pretreatment with opiates on

feeding and drinking. If tolerance develops to opiate-induced modifications of intake, then the effect of the drug pretreatment should dissipate over trials.

The early experiments that addressed this question suggested that tolerance does not develop to opiate-induced modifications of intake. Jalowiec et al. (1981) reported that the suppressant effect of daily injections of naloxone (2.5 mg/kg), as well as chronic infusions via osmotic mini-pumps, on the intake of food and water was maintained across 6 - 8 test days. Upon termination of drug treatment, food intake gradually returned to normal without any compensatory overeating. Furthermore, Lynch (1986) and Lynch and Burns (1990) demonstrated that daily injections of naloxone, 30 min prior to a presentation of sucrose or saccharin solution, produced suppressed intake of these solutions that was maintained across a 10 day period, without the development of tolerance. Upon termination of the naloxone treatment, however, Lynch and Burns (1990) reported a compensatory increase in the intake of sucrose, but not saccharin solution, for a 5 day period. These reports consistently failed to demonstrate tolerance to the suppressant effects of naloxone on intake.

More recently, Goodison and Siegel (1992) have demonstrated tolerance to the anorexic effect of naloxone on sucrose intake with a compensatory increase in sucrose intake on saline pretreatment test trials. They suggest that this effect represents not only the establishment of tolerance to the anorexigenic properties of naloxone, but also the establishment of a drug-opposite compensatory conditioned response elicited by the taste of sucrose. This effect is thus consistent with

Siegel's (1978) compensatory conditioning model of drug tolerance.

According to Siegel, tolerance is mediated by a conditioned compensatory response to the effects of a drug and can be explained within the Pavlovian (Classical) Conditioning paradigm. In the Pavlovian Conditioning paradigm a conditioned stimulus (CS), for example a tone, predicts the occurrence of an unconditioned stimulus (UCS), for example food, which causes an unconditioned response (UCR), for example salivation. Eventually, the CS becomes capable of eliciting a conditioned response (CR) which mimics the UCR, as a result of the pairing of the CS with the UCS. Thus, for example, the presentation of the CS alone elicits the CR of salivation.

Siegel (1978) proposed that drug tolerance could be explained by a Pavlovian conditioning mechanism. Siegel's model assumes that with repeated presentations of a drug, the UCS, cues present at the same time that the drug is experienced, become CSs associated with the drug. The CRs elicited by these CSs, however, act to compensate for the effect of the drug. The CRs are thus opposite to the UCR. Since the CRs compensate for the effects of the drug itself, those responses reduce the reaction otherwise elicited by the drug. Therefore, the response to the drug is attenuated when the drug is taken in the presence of these conditioned stimuli. The evidence in support of such a model of tolerance was reviewed in Siegel (1989).

While the original associative model of tolerance, as proposed by Siegel, received extensive support, it was unable to explain the occurrence of contingent

tolerance. Contingent tolerance refers to the phenomenon whereby the placing of a specific behavioral demand on a drug-affected system is seen to affect the development of tolerance to the drug under consideration. For example, LeBlanc, Gibbins and Kalant (1973,1975) accelerated the rate of development of tolerance to motor impairment produced by alcohol by placing motoric demands on rats exposed to alcohol. These authors proposed that the functional disturbance experienced in the drug state is responsible for the development of tolerance. Thus, engaging in motor activity while under the influence of alcohol increased the functional disturbance caused by alcohol, augmenting the development of tolerance. Research on contingent tolerance has shown that behavioral demands govern tolerance development (Poulos & Cappell, 1991). Tolerance does not develop in response to the mere systemic presence of a drug because this in itself does not constitute a functional disturbance for the organism. The organism must interact with relevant features of the environment for a drug effect to be biologically detected as a functional disturbance.

A revised formulation of the Pavlovian analysis of tolerance has attempted to account for contingent tolerance. According to this reconceptualization, the UCS is the functional disturbance in a physiological system produced by the drug, and the UCR is the adaptive reaction to the homeostatic disturbance produced by the drug's action (Eikelboom & Stewart, 1982; Poulos & Cappell, 1991). The UCR can only be elicited if the action of the drug produces a functional disturbance (UCS). For example, in the case of morphine-induced analgesia, the

analgesic disturbance caused by morphine is the UCS which evokes the UCR of hyperalgesia or increased sensitivity to pain as an adaptive response. In turn, this hyperalgesic UCR provides a basis for a compensatory hyperalgesic CR after pairings with predictive CSs through Pavlovian processes. Theoretically, therefore, conditioned tolerance is no different than other types of Pavlovian conditioning, because the CR mimics the UCR. Hence, the development of tolerance is mediated by the compound effects of the UCR and the CR which counteract the functional disturbance caused by morphine. Notably, although hyperalgesia is the UCR elicited by the functional disturbance of analgesia caused by morphine, it is not observed initially. Over time, with conditioning, the hyperalgesic response that mediates tolerance becomes apparent as the CR and the UCR summate.

Recently Goodison and Siegel (1992) utilized this model of contingent tolerance to demonstrate tolerance to the suppressant effects of naloxone on sucrose intake. On repeated conditioning trials, rats received an injection of naloxone or saline 30 min prior to receiving a bottle containing a 10% sucrose solution in their home cage. Twenty-four hours later the rats received non-contingent injections of the solution that they did not receive on the conditioning trial, in the same home-cage environment. Goodison and Siegel (1992) reported that tolerance developed to the suppressant effect of naloxone on sucrose intake. Furthermore, they demonstrated, in a saline probe test after conditioning, that the naloxone conditioned rats drank more sucrose solution than the saline conditioned

rats. This effect was interpreted as a compensatory CR elicited by the taste of sucrose (CS) in the naloxone conditioned rats. Rats thus appear to become tolerant to the anorexic properties of naloxone and this tolerance appears to be mediated by the formation of a compensatory CR. Such a mechanism may also account for the facilitation in sucrose intake following repeated naloxone-sucrose pairings previously reported by Lynch and Burns (1990). It is not clear, however, whether the CR reflects a modification in the palatability of the sucrose solution or some other factor. The taste reactivity test used as a measure in this paradigm might shed some light on this issue.

Taste Reactivity as a Tool for Assessing Tolerance to the Effects of Morphine on Palatability

Traditionally, investigations of the influence of drug pretreatment on ingestion have relied on intake measures. One major problem with this approach is that it is difficult to ascertain whether intake is truly a function of palatability or of some other factor. Intake tests measure both appetitive (tendency to approach the bottle) and consummatory behaviours (consumption of solution). Factors other than palatability, such as deprivation condition, the presence or absence of contextual cues, and internal emotional states, may influence a rat's likelihood to approach a bottle. In an effort to circumvent this issue, Grill and Norgren (1978) developed the taste reactivity test, which exclusively measures the consummatory component of responding to a taste. With this test, palatability is determined by

specific action patterns (e.g., tongue protrusions, mouth movements, gapes) which follow exposure to taste stimuli, rather than simply relying on intake.

Furthermore, although standard intake tests can be effective measures of the preference for foods and liquids that rats readily consume, such as sucrose solution, they are less effective measures of the preference for foods and liquids that rats are reticent to consume, such as quinine solution. Since control rats consume little quinine, drug-induced modification of baseline intake is difficult to assess. On the other hand, the taste reactivity test serves as an effective measure of quinine palatability without the problem of floor effects in intake. The more aversive the quinine, the greater the strength of aversive taste reactivity responses.

During the taste reactivity test, the oral and somatic responses of animals are recorded following contact with different taste stimuli. These responses can be classified as ingestive, neutral or aversive. Highly palatable solutions, such as sucrose, elicit ingestive responses which include tongue protrusions, paw licking and mouth movements. Unpalatable solutions, such as quinine, elicit aversive responses which include chin rubbing, paw treading and gaping (Grill, 1985). Finally, neutral solutions such as water (in a nondeprived rat) elicit predominantly passive drips. Hence, using the taste reactivity test, the palatability of taste stimuli can be measured by the extent to which these stimuli elicit an ingestive, neutral or aversive pattern of responding.

Parker et al. (1992) used the taste reactivity test to investigate the effect of morphine and naltrexone on the palatability of sucrose and quinine solutions.

Based on the putative ability of morphine to enhance the pleasant properties and reduce the aversive properties of taste stimuli (Lynch & Libby, 1982), Parker et al. (1992) anticipated that morphine would decrease the aversive responses elicited by quinine and increase the ingestive responses elicited by sucrose. In contrast, it was expected that naltrexone would increase the aversive responses elicited by quinine and decrease ingestive responses elicited by sucrose.

In their investigation of the effects of morphine on taste reactivity, Parker et al. (1992) pretreated rats with morphine (2 mg/kg, sc), 30 min prior to administering an infusion (via an intraoral catheter) of either .05% quinine or 20% sucrose solution over a 10 min period. Their results indicated that the morphine-pretreated rats displayed fewer aversive taste reactivity responses than the saline-pretreated rats when infused with 0.05% quinine solution. Hence, morphine appeared to reduce the aversiveness of quinine. This effect was subsequently replicated and extended to a higher quinine concentration (.1%) and to familiar as well as novel quinine. Morphine consistently reduced aversive taste reactions and enhanced neutral passive drips elicited by quinine infusions. This pattern of reactions suggests that morphine shifted the palatability of quinine from highly aversive to mildly aversive/neutral.

Contrary to expectations, however, morphine did not increase ingestive reactions elicited by sucrose solution. Notably, Evans and Vaccarino (1990) did report a stimulatory effect of morphine on the intake of saccharin. In contrast, however, Lynch and Libby (1983) failed to observe such an effect using a two-

bottle intake test. Lynch and Libby (1983) found that morphine enhanced saccharin intake only when the concentration of saccharin rendered the taste as predominantly bitter. They proposed that the effect of morphine is to suppress the bitter taste of saccharin solutions rather than to enhance the sweet taste. Siviy et al. (1982) also presented a similar argument when they noted that a 2 mg/kg dose of morphine caused an increase in the intake of a highly concentrated 0.5% saccharin solution, while being ineffective at modifying the intake of lower saccharin concentrations. Siviy et al. (1982) concluded that morphine may be working to reduce the aversive qualities of higher concentrations of saccharin, thus increasing preference for it. This suggestion can be used to explain the failure of morphine to enhance ingestion of sucrose observed by Parker et al. (1992) in the experiment under review. Since sucrose is nonaversive, morphine would not be expected to enhance its intake.

Doyle, Berridge and Gosnell (1993), however, reported that when a high dose of morphine (4 mg/kg, sc) was administered 2 hr, rather than 30 min, prior to an infusion of a sucrose/quinine mixture (7% sucrose/.01% quinine), morphine enhanced the palatability of that tastant. The enhanced palatability was the result of an increase in the ingestive reactions without a decrease in aversive reactions, suggesting that morphine selectively enhanced the palatability of sucrose without modifying quinine palatability. The quinine concentration of .01%, however, produced few aversive reactions, suggesting that floor effects may have prevented a detection of a morphine-induced decrease in aversive reactivity as reported by

Parker et al. (1992) with the use of .05% quinine and a longer test period. Finally, Rideout and Parker (unpublished manuscript) have recently demonstrated that morphine (2 mg/kg, sc) does increase the palatability of 2% and 20% sucrose solutions, when administered 30 min or 2 hours prior to the intraoral infusion. The difference between Parker et al. (1992) and Rideout and Parker's procedure was predominantly due to the duration of adaptation training to the taste reactivity test apparatus. Parker et al. (1992) employed only a single taste reactivity adaptation trial, but Rideout and Parker employed three adaptation trials. Apparently the ability of rats to demonstrate morphine-induced enhancement of sucrose palatability depends upon their being tested in a familiar environment. This suggests that the effect is relatively weak as compared with the more robustly demonstrated suppression of aversive responding to quinine.

Parker et al. (1992) also investigated the effect of pretreatment with naltrexone (1 mg/kg) on the palatability of two sucrose concentrations, 2% and 20%, and on 0.05% quinine. The saline and naltrexone pretreated rats did not display any significant differences in pattern of responding when infused with 0.05% quinine. Naltrexone, however, did suppress the ingestive responding elicited by both concentrations of sucrose solution. In addition, the naltrexone-pretreated rats displayed more passive drips than the saline-pretreated rats. These results indicate that naltrexone reduced the positive hedonic assessment of sucrose, regardless of whether that solution was highly palatable (20% sucrose) or mildly palatable (2%). Doses as low as .1 mg/kg of naltrexone were subsequently found

to be sufficient to reduce the positive palatability of 2% sucrose solution.

According to evidence from the taste reactivity test, the effect of opiates on feeding is mediated by changes in the palatability of tastants. In these experiments, morphine reduced the aversive responses elicited by a quinine solution (Parker et al., 1992) and enhanced ingestive responding elicited by a sucrose solution (Doyle et al., 1993; Rideout & Parker, unpublished manuscript). Naltrexone reduced the ingestive responses elicited by a highly palatable and a mildly palatable sucrose solution (Parker et al., 1992). Hence, morphine may increase intake by both reducing the aversive, and enhancing the hedonic properties of food, while naltrexone may reduce intake by reducing the pleasant properties of the taste of food. Therefore, in accord with consumption test results, evidence provided by the taste reactivity test supports the contention that the enhancing or inhibitory effect of opiate agonists and antagonists on feeding may be a function of changes in the palatability of tastants (Cooper, 1983; Lynch & Libby, 1983; Parker et al., 1992).

Thus far, studies employing the taste reactivity test have investigated the effect of acute morphine exposure on palatability, leaving the subject of the effect of chronic morphine exposure on the palatability of tastants virtually unexplored. Notably, chronic exposure to morphine has been reported to produce tolerance in other physiological systems, for example the analgesic system, (e.g., Jaffe & Martin, 1990; Siegel, 1989). Based on this observation, it is thus conceivable that chronic exposure to morphine may also produce tolerance to morphine-induced changes in palatability.

Experiment 1

Experiment 1 was designed to determine whether tolerance develops to the morphine-induced suppression of aversive taste reactions elicited by quinine; and furthermore, if tolerance does develop, whether this tolerance is mediated by a compensatory conditioned response (Siegel, 1978). Rats received eight conditioning trials during which taste-reactivity responses were assessed. During the conditioning trials, the Contingent group was injected with morphine, and the Noncontingent group with saline, 30 min prior to receiving an intraoral infusion of a quinine solution. Twenty-four hours after each conditioning trial, the Noncontingent group received a morphine injection and the Contingent group received a saline injection, 30 min prior to placement in the taste reactivity chamber without the quinine infusion. Three days after the third and eighth conditioning trials, all rats received a saline test trial during which they were injected with saline 30 min prior to receiving the quinine infusion in order to assess the compensatory CR elicited by quinine. If tolerance developed and a compensatory CR was responsible for tolerance, then quinine should be more aversive to the Contingent group than to the Noncontingent group on the saline test trial.

In the language of the homeostatic theory of drug tolerance (Poulos & Cappell, 1991) the UCS is the morphine-induced reduction of quinine aversiveness and the UCR is the adaptive compensatory increase in quinine aversiveness. The CS, the taste of quinine, comes to elicit the compensatory CR of increased aversiveness of quinine after repeated pairings with the UCS, the morphine-induced attenuated

aversiveness. It was anticipated that tolerance would develop to morphine-induced changes in the palatability of quinine such that when the CS was presented alone, without prior exposure to morphine, the compensatory reaction of quinine-elicited enhanced aversiveness would be unmasked. The Contingent group would, therefore, demonstrate more aversive taste reactions to the quinine solution than the Noncontingent group.

Method

Subjects

Subjects were 23, experimentally-naive, male Sprague-Dawley rats, purchased from Harlan-Sprague Dawley Breeding Laboratories, Indianapolis, IN, weighing 210 - 260g at the start of the experiment. They were maintained on ad lib rat chow and water throughout the experiment, and were housed individually in stainless steel cages. The housing-room was illuminated on a 12:12 hr light-dark schedule.

Procedure

Surgery. One week after arriving in the laboratory, the rats were implanted with intraoral cannulae as previously described by Parker (1980). After being deprived of water for 24 hr, each rat was anaesthetized with atropine (0.5 mg/kg, ip), followed by ketamine (100 mg/kg, ip) and xylazine (3 mg/kg, ip) 15 min later. A 15-gauge, thin-walled, stainless steel needle was inserted through the rat's skin in the mid-neck region, brought subcutaneously behind its ear along the inside of the cheek, and exited through the soft part of its cheek behind the first molar. The skin around each of the punctured sites was swabbed with iodine.

With the needle in place, a 10.2 cm length of polyethylene tubing was inserted through the barrel. The needle was then removed, and the tubing was secured at the neck by a 20-gauge intramedic adapter, and in the mouth by a 5 mm plastic washer.

Taste Reactivity Testing. One week after recovering from surgery, the rats were given taste reactivity adaptation training. For the adaptation trials, each rat was placed in the glass taste reactivity test chamber (22.5 x 26.0 x 20.0 cm). The room was illuminated by four 100-W light bulbs with two on either side of the chamber and two aimed at a mirror below the chamber. Once the animal was placed in the chamber, its cannula was connected to an infusion pump (Harvard Apparatus, Model 22) by a 35 cm long tube. One minute later, the rat received a 5 ml intraoral infusion of water at the rate of 1 ml/min for 5 min.

After 3 days of adaptation trials, the rats received taste reactivity conditioning trials. These conditioning trials were identical to the adaptation trials, except that the rats received an injection (1 ml/kg) of 2 mg/ml morphine, sc, (Contingent group, n = 12) or of saline solution (Noncontingent group, n = 11), 30 min before receiving a 5-ml intraoral infusion of .05% (6.7×10^{-3} mol) quinine solution at the rate of 1 ml/min for 5 min, in the taste reactivity chamber. Immediately prior to the injection, each rat's food and water were removed and were returned one hour later. The taste reactivity conditioning trials were conducted 72 hrs apart. On the days immediately following conditioning trials, all rats received noncontingent trials. On the noncontingent trial, each rat's food and

water were again removed immediately before the Contingent group of rats received saline injections, and the Noncontingent group received morphine injections, in the same dosage and concentrations as during conditioning. Thirty minutes later, they were placed in the taste reactivity chamber for 5 min. The rats were treated identically on the noncontingent trials as on the conditioning trials except that they were not infused with any solution following the injection. Subjects were given a rest day after the noncontingent day and prior to the next conditioning day. A total of eight conditioning trials were conducted.

Three days after the third and eighth conditioning trials, the rats received a test trial. During each of these test trials, all of the rats were injected with saline (1 ml/kg), 30 min prior to a 5 min infusion of quinine. Food and water were removed and returned as during the conditioning trials. For statistical purposes these test trials were treated as discrete events and analyzed individually since they represented two separate attempts to assess the development of tolerance.

During each conditioning trial and test trial, the orofacial and somatic responses of each subject were recorded on videotape, with a camera which focused on a mirror beneath the chamber that was hung at an angle to facilitate viewing of the rat's ventral surface.

Scoring of Behavioral Categories

The videotapes of the taste reactivity test were scored in real time by a rater who was unaware of the experimental conditions. Four behavioral indices were assessed: aversive reactions, neutral/mildly aversive reactions, ingestive

reactions and activity.

Aversive Reactions. The behavioral category of aversive reactions was comprised of the combined frequency of five aversive taste reactions: chin rubbing (forward projection of the head with the chin rubbing against a substrate), gaping (triangular, wide opening of the mouth), paw treading (rhythmic pushing of the forepaws against the floor of the cage), limb flicking (rapid shaking of the forelimbs) and head shakes.

Neutral/Mildly Aversive Reactions. The behavioral category of neutral/mildly aversive reactions was comprised of the frequency of passive drips (number of drops of the test solution that drip from the rat's mouth to the floor when the rat is not actively ejecting the solution by an aversive response).

Ingestive Reactions. The behavioral category of ingestive reactions represented the duration (sec) of the display of three ingestive reactions. tongue protrusions (extension of the tongue), mouth movements (movements of the mouth without extensions of the tongue) and paw licks.

Activity. The behavioral category of activity represented the frequency of the display of rearing (occurrences of vertical movements with both forelimbs off the floor of the chamber) and active locomotion (occurrences of horizontal movements along the floor of the chamber with both forepaws on the floor) throughout the infusion period.

Results

Conditioning Trials

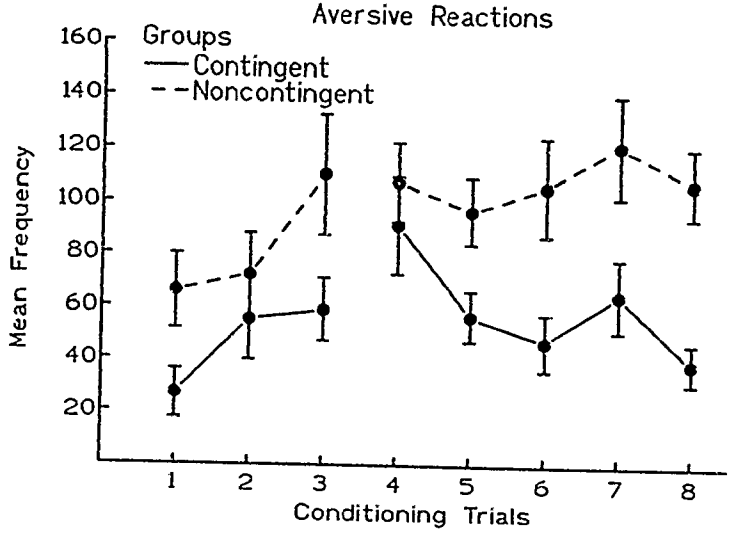
Figure 1 presents the mean frequency or duration of aversive reactions, passive drips, ingestive reactions and activity, across conditioning trials, for the Contingent and the Noncontingent groups. Separate 2 by 8 (Group x Conditioning Trials) mixed factor ANOVAs revealed a significant Group effect for aversive reactions, $F(1, 21) = 15.81$, $p < .01$, and for ingestive reactions, $F(1,21) = 7.9$, $p < .05$. The Contingent group displayed fewer aversive reactions and spent more time exhibiting ingestive reactions, than did the Noncontingent group across the conditioning trials. The groups, however, did not differ on the basis of the frequency of passive drips and activity elicited by the quinine solution. Notably, the mixed factor ANOVAs did not reveal any significant Group by Trials interactions for the assessed behaviours.

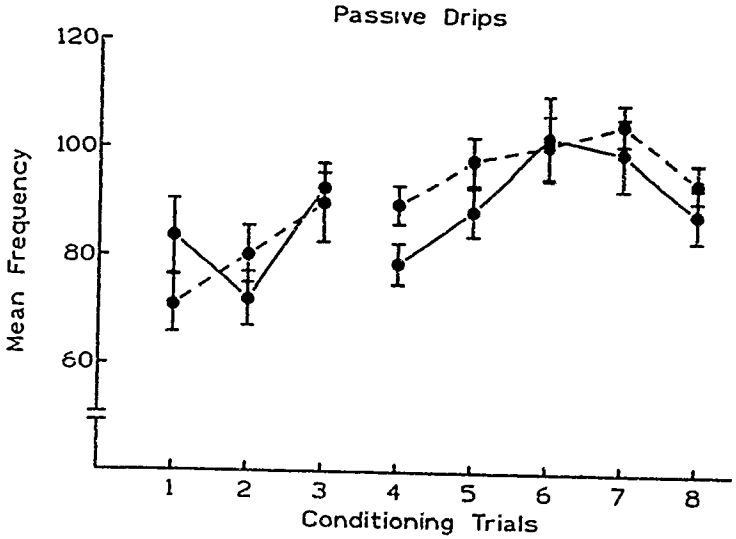
The mixed factor ANOVAs also revealed a significant Trials effect for aversive reactions, $F(7,147) = 3.13$, $p < .01$, passive drips $F(7,147) = 8.63$, $p < .01$ and activity $F(7,147) = 15.46$, $p < .01$. Subsequent Newman-Keuls pairwise comparisons revealed that overall the Contingent and Noncontingent groups displayed fewer aversive reactions on Trial 1 than on Trials 3, 4 and 7 ($ps < .05$). The Contingent and Noncontingent groups also displayed fewer passive drips on Trials 1 and 2 than on Trials 4 - 8, and on Trial 4 than on Trials 6 and 7 ($ps < .05$). The Contingent and Noncontingent groups collectively engaged in less activity on Trials 1 and 2 than on any other trial ($ps < .05$).

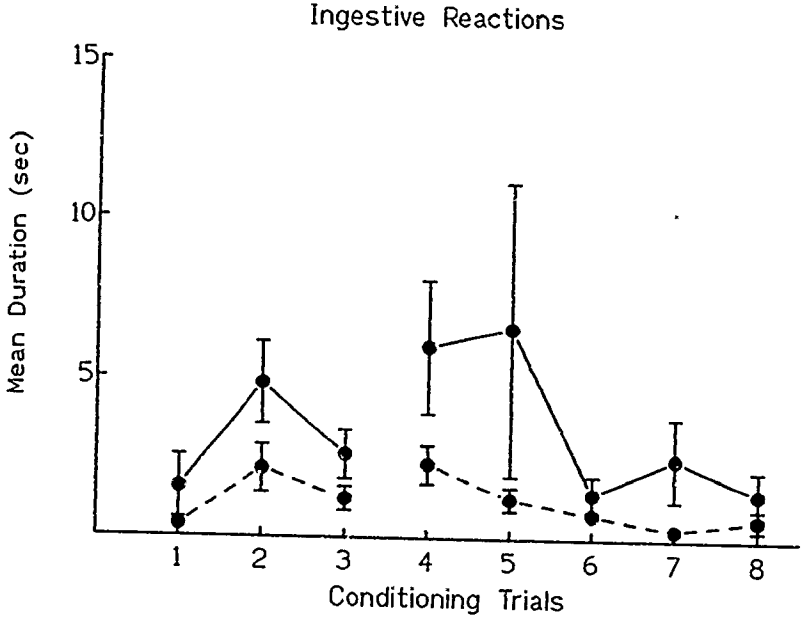
Test Trials

Figure 2 presents the mean frequency or duration of aversive reactions, passive drips, ingestive reactions and activity elicited by quinine solution during each test trial of Experiment 1. Test 1 was conducted after three conditioning trials and Test 2 was conducted following eight conditioning trials. The Contingent group displayed significantly fewer aversive taste reactions during the quinine infusion than the Noncontingent group during Test 1, $t(21) = 1.8$, $p < .05$, and during Test 2, $t(21) = 2.7$, $p < .01$. The groups did not differ in the mean frequency or duration of any of the other behaviours on either test.

Figure 1. Mean frequency or duration of aversive reactions, passive drips, ingestive reactions and activity on the conditioning trials of Experiment 1.


Aversive Reactions
Groups
Contingent
Noncontingent
Mean Frequency
160
140
120
100
80
60
40
20
1
2
3
4
5
6
7
8
Conditioning Trials


Passive Drips
Mean Frequency
120
100
80
60
1
2
3
4
5
6
7
8
Conditioning Trials


Ingestive Reactions
Mean Duration (sec)
15
10
5
1
2
3
4
5
6
7
8
Conditioning Trials

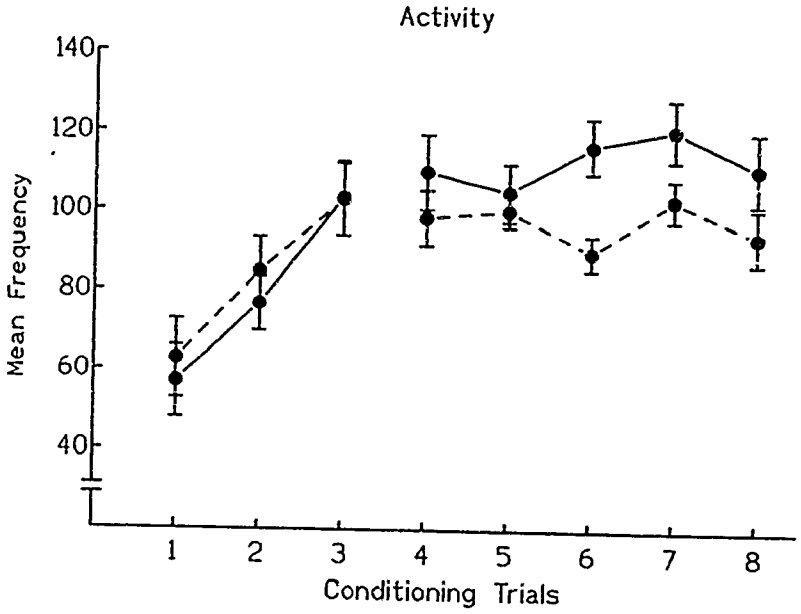
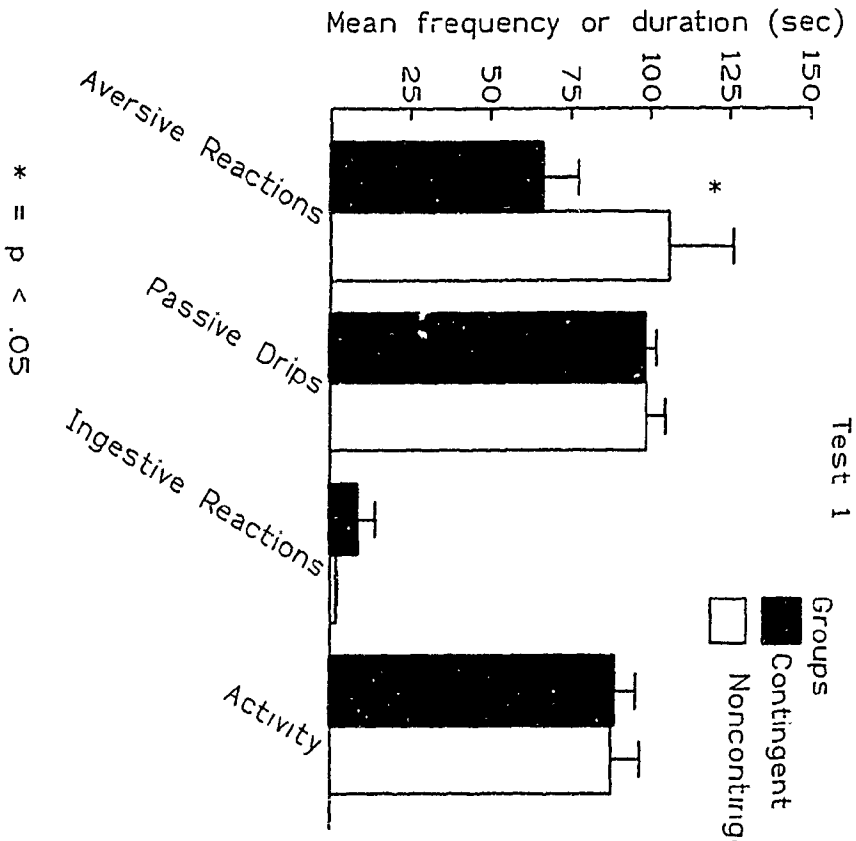
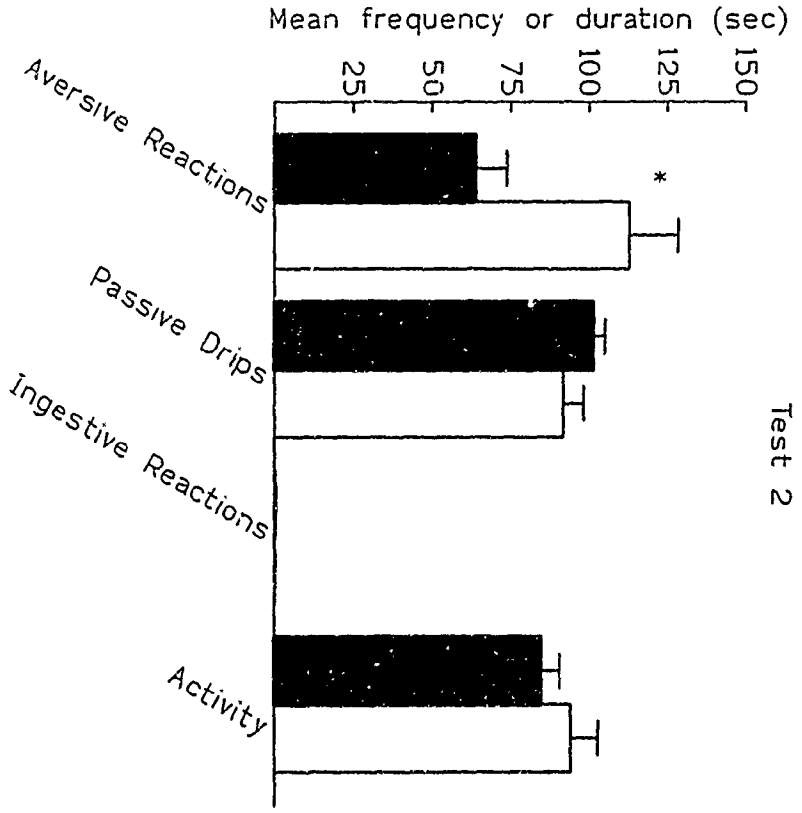

Activity
Mean Frequency
140
120
100
80
60
40
1
2
3
4
5
6
7
8
Conditioning Trials

Figure 2. Mean frequency or duration of aversive reactions, passive drips, ingestive reactions and activity on the test trials of Experiment 1.


Mean frequency or duration (sec)
25
50
75
100
125
150
Aversive Reactions
Passive Drips
Ingestive Reactions
Activity
*
Groups
Contingent
Noncontingent
Test 1
* = p < .05


Mean frequency or duration (sec)
25
50
75
100
125
150
Aversive Reactions
Passive Drips
Ingestive Reactions
Activity
*
Test 2

Discussion

As previously reported with acute exposure to morphine (Parker et al., 1992), morphine pretreatment reduced the frequency of aversive reactions elicited by quinine solution. Additionally, morphine pretreatment enhanced the duration of ingestive reactions displayed during quinine infusion, but did not modify activity level. These results strongly support the contention that morphine modifies the palatability of quinine by reducing its aversive taste properties. Since the Group by Trial interaction was not significant for any behaviour, the results also suggest that tolerance was not established to morphine-induced modifications of quinine palatability.

The test trials of Experiment 1, however, revealed evidence of drug-similar CRs. During the conditioning trials, the Contingent group displayed fewer aversive responses than the Noncontingent group during the quinine infusion. During the test trial, the Contingent group also displayed similar suppressed aversive reactions when infused with quinine in the absence of morphine pretreatment. This suggests that the effects of morphine became associated with the quinine CS resulting in suppressed reactions or drug-like CRs.

Experiment 2

Experiment 1 revealed that chronic pretreatment with morphine did not produce tolerance to morphine-induced modification of quinine palatability. Furthermore, after only three conditioning trials the rats displayed drug-similar conditioned attenuation of quinine aversiveness during the saline test trial.

Experiment 2 assessed whether such conditioning would occur after a single conditioning trial. In order to facilitate one trial conditioning, the duration of quinine exposure was increased to 10 min, a manipulation previously demonstrated to produce a stronger morphine-induced modification of quinine palatability now evident in a 5 min infusion of quinine (Parker et al., 1992).

Method

Subjects

Subjects were 24 male, Sprague-Dawley rats, which weighed 210-270g at the start of the study. They were treated in an identical manner to those of Experiment 1.

Procedure

One week after recovering from surgery the rats were given three adaptation trials following the procedures used in Experiment 1.

After the three days of adaptation trials, the rats received one taste reactivity conditioning trial. Thus, rats received a subcutaneous injection (1 ml/kg) of 2 mg/kg morphine (Contingent group, n = 12) or of saline (Noncontingent group, n = 12), 30 min before receiving a 10 ml intraoral infusion of .05% (6.7×10^{-3} mol) quinine solution at the rate of 1 ml/min for 10 min, in the taste reactivity chamber. Immediately prior to the injection each rat's food and water were removed for an hour. On the day following the conditioning trial, all rats received a noncontingent trial. On the noncontingent trial, food and water were removed and the Contingent group of rats received saline injections, while the Noncontingent group received

morphine injections, in the same dosages and concentrations as during conditioning. Thirty minutes later the rats were placed in the taste reactivity chamber for 10 min. The rats were treated in the same way as during the conditioning trial except that they were not infused with quinine solution. Thirty minutes later the food and water were returned. On the second day following the noncontingent trial the rats received a test trial. During this trial all of the rats were injected with saline, 30 min prior to a 10 min infusion of quinine. Food and water were removed and returned as during the conditioning trial.

Results

Figure 3 presents the mean frequency or duration of aversive taste reactions, passive drips, ingestive reactions and activity displayed on the conditioning trial of Experiment 2. The Contingent group displayed significantly fewer aversive reactions, $t(21) = 4.18$, $p < .01$, and less activity, $t(21) = 2.51$, $p < .01$; and, significantly more passive drips, $t(21) = 2.12$, $p < .05$, than the Noncontingent group during the conditioning trial. There was no significant difference between the Contingent and Noncontingent group with respect to mean frequency of ingestive responses.

Figure 4 presents the mean frequency of aversive reactions, passive drips, ingestive reactions and activity displayed by the Contingent and Noncontingent groups on the test trial of Experiment 2. The Contingent and Noncontingent groups did not differ in the frequency or duration of any behavioral category. It should also be noted that the pattern of results of the conditioning and test trial of Experiment 2 did not differ when the data were separated and analyzed in two 5 min blocks.

Figure 3. Mean frequency or duration of aversive reactions, passive drips, ingestive reactions and activity on the conditioning trial of Experiment 2.

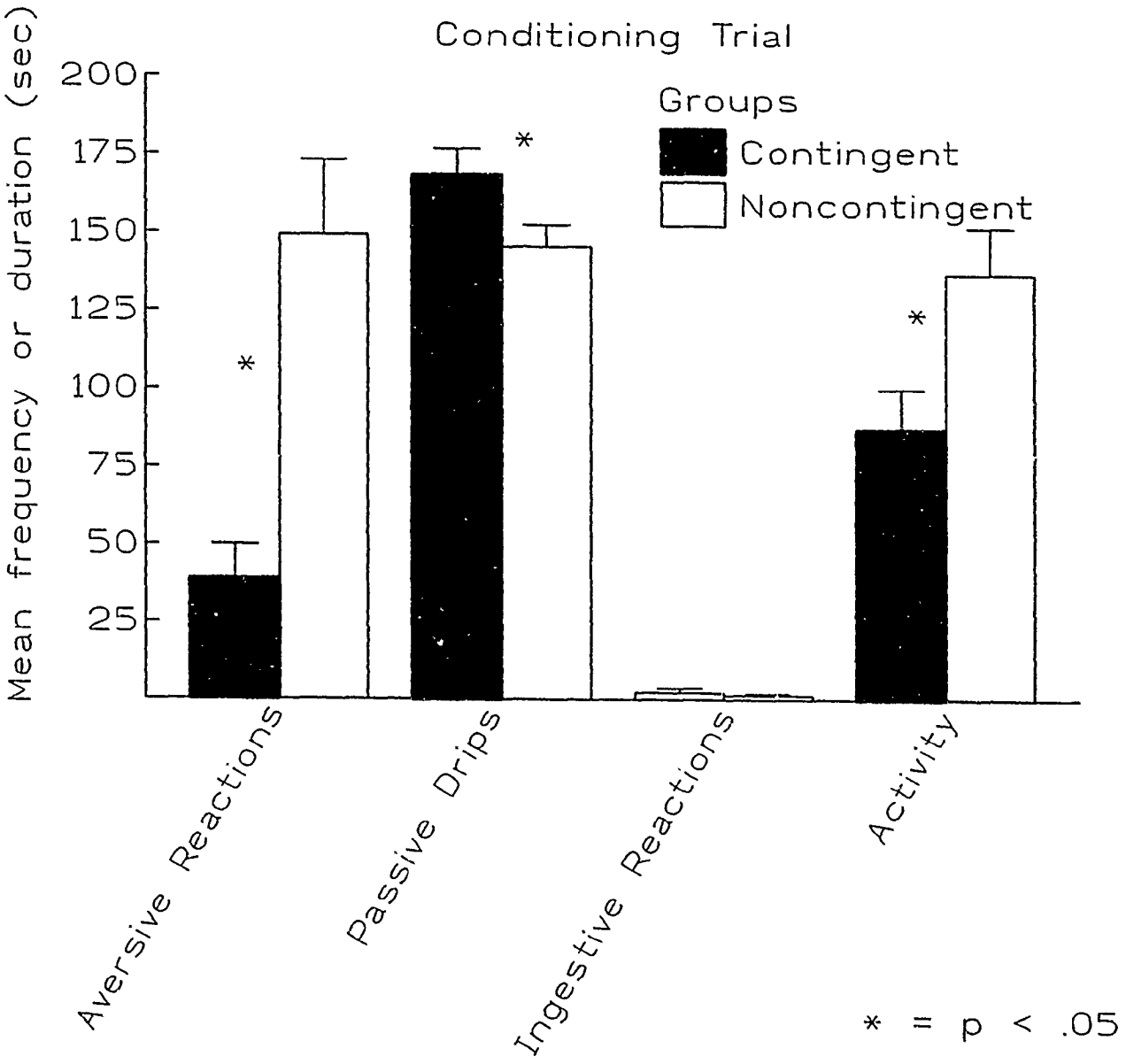
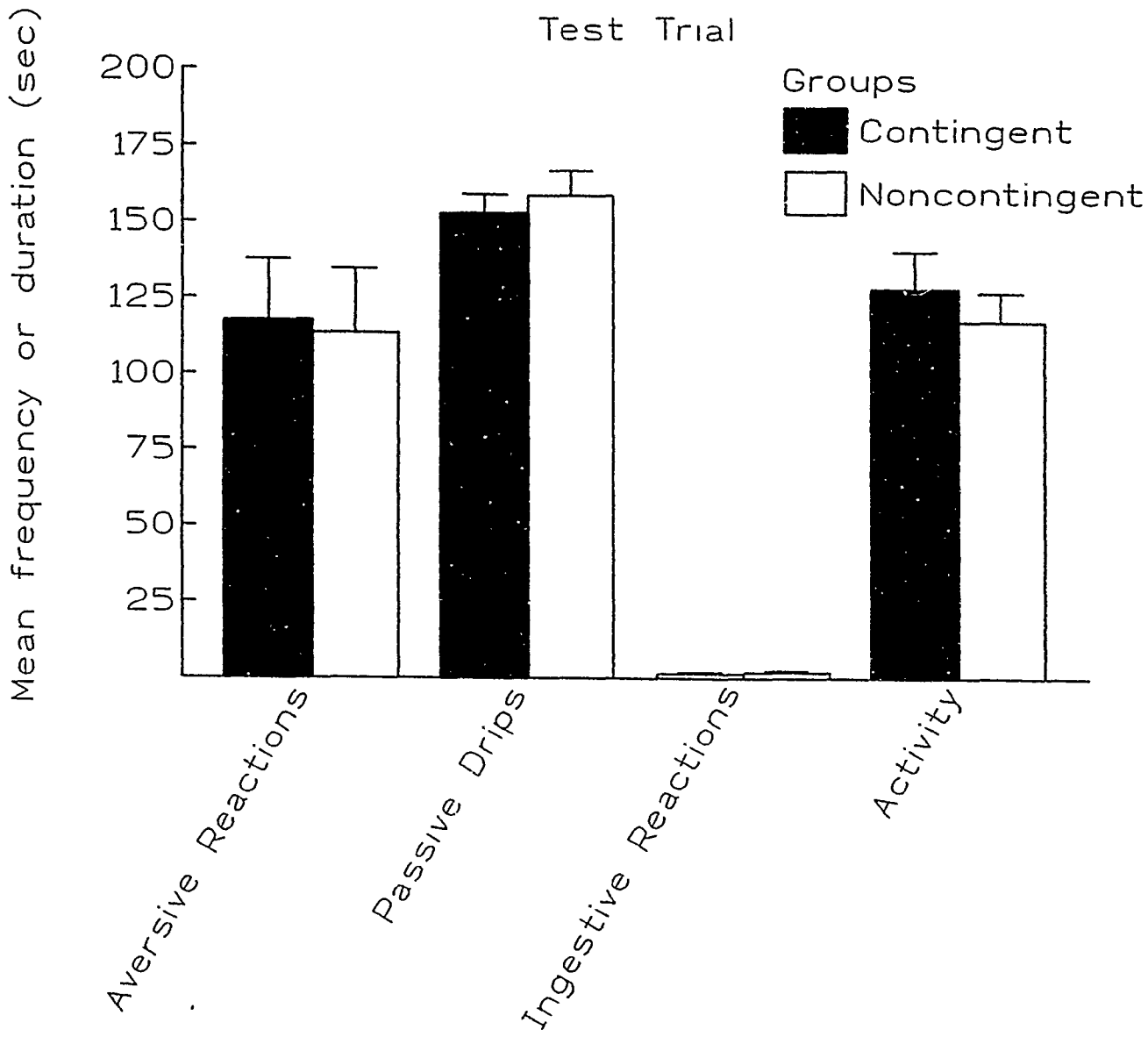

Conditioning Trial
Groups
Contingent
Noncontingent
Mean frequency or duration (sec)
200
175
150
125
100
75
50
25
*
*
*
Aversive Reactions
Passive Drips
Ingestive Reactions
Activity
* = p < .05

Figure 4. Mean frequency or duration of aversive reactions, passive drips, ingestive reactions and activity on the test trial of Experiment 2.


Test Trial
Groups
Contingent
Noncontingent
Mean frequency or duration (sec)
200
175
150
125
100
75
50
25
Aversive Reactions
Passive Drips
Ingestive Reactions
Activity

Discussion

Morphine attenuated quinine aversiveness as previously reported (Parker et al., 1992) and as was evident in Experiment 1. The modification of quinine palatability is apparent from the suppression of aversive reactions and the enhancement of mildly aversive/neutral passive drip reactions displayed by the Contingent group. Additionally, with a 10 min infusion trial, the Contingent group displayed suppressed activity when compared with the Noncontingent group. Notably, morphine is known to produce a suppression in overall activity (Jaffe & Martin, 1990). The length of the test period in this experiment may have increased the likelihood of observing such a suppression in activity.

The results of the test trial of Experiment 2 suggest that a single conditioning trial is not sufficient to establish conditioned drug-like responses. Experiment 1 demonstrated, however, that 3 trials, with a 5 min quinine exposure during conditioning, do produce conditioned attenuation of aversive reactivity to quinine.

General Discussion

The primary purpose of this study was to determine whether tolerance would develop to morphine-induced changes in the palatability of quinine, as a result of multiple contingent morphine-quinine trials. Previous findings indicate that acute exposure to morphine reduces the aversiveness of quinine solution (e.g., Parker et al., 1992). If tolerance develops to this effect, then one would expect that with repeated exposures, morphine would fail to attenuate aversive reactions to the taste

of quinine. Contrary to expectations, however, the pattern of results observed in this study suggests that tolerance does not develop to morphine-induced modifications of the palatability of quinine. In Experiment 1, across eight conditioning trials, morphine maintained its ability to attenuate the aversive taste properties and to enhance the hedonic taste properties of the .05% quinine solution.

The failure to observe tolerance to morphine-induced modifications of quinine palatability is consistent with the findings of previous research designed to assess the development of tolerance to opiate-induced modifications of the palatability of taste stimuli (e.g., Jalowiec et al., 1981; Lynch & Burns, 1990). Jalowiec et al. (1981) did not observe tolerance to the suppressant effect of naloxone on the food intake of deprived rats. Similarly, Lynch and Burns (1990) reported a lack of the development of tolerance to naloxone-induced suppression of the intake of a 20% sucrose solution and a 0.1% saccharin solution by deprived rats.

According to Wolgin and Benson (1990), however, the development of tolerance to opiate-induced changes in the palatability of taste stimuli may be mediated by the "novelty" of the taste. Wolgin and Benson (1990) reported evidence of tolerance to morphine-induced effects on the consumption of sweetened condensed milk in rats which had been given prior experience with this tastant. Similarly, Goodison and Siegel (1992) reported evidence of tolerance to naloxone-induced suppression of the intake of a familiar 10% sucrose solution. These findings suggest that the novelty of the taste stimuli may hinder the development of tolerance to opiate-induced changes in the palatability of that tastant.

It must be noted, however, that those studies which have reported evidence of tolerance to opiate-induced changes in the palatability of tastants have generally relied on simple intake measures whereby experimenters monitor the amount of test solution that is consumed. One major problem with this method of assessment is that it is difficult to ascertain whether intake is truly a function of palatability or of some other factor. Intake measures assess both appetitive (ability to approach test solution) and consummatory behaviours. Factors other than palatability, including deprivation conditions, and the emotional state of the animal, may influence its likelihood to approach a bottle and consume its contents. The taste reactivity test employed in the present study is a more direct method of assessing palatability since appetitive factors are eliminated. Based on this measure it appears that tolerance does not develop to morphine-induced changes in the palatability of novel quinine.

The results of the present study also provide evidence that quinine became conditionally less aversive as a result of the contingent morphine-quinine pairing. During the conditioning trials of Experiment 1, the Contingent group displayed suppressed aversive reactions to quinine in comparison to the Noncontingent group. After only three conditioning trials, the Contingent group displayed similar suppressed aversive reactions to quinine, in the absence of morphine pretreatment. This observation suggests that the effects of morphine became associated with the quinine CS, resulting in suppressed aversive reactions or drug-like CRs. This effect was also evident after eight conditioning trials in Experiment 1. Experiment 2, however, revealed that a single 10 min conditioning trial was insufficient to produce

this conditioned effect.

The phenomenon of drug-similar CRs has been conceptualised in the model of conditioning proposed by Eikelboom and Stewart (1982). According to these researchers, CRs always mimic UCRs. The type of responses elicited, however, depends on whether the UCS, that is, the drug stimulus, acts on the *afferent* or *efferent* arms of negative regulatory feedback systems in the central nervous system (CNS). Conceptually, the regulatory negative feedback system is made up of *sensors* which measure incoming signals or stimuli, *integrators* which determine whether the incoming signals are at an appropriate level, and *effectors* which act as homeostatic mechanisms to return incoming signals to appropriate levels. The *sensors* and *integrators* comprise the *afferent* arm, while the *effectors* comprise the *efferent* arm of the feedback system.

According to Eikelboom and Stewart (1982) when a drug acts on the *afferent* arm of a feedback system, the drug-induced neural signal is the UCS and the observed drug effect is the UCR. The CR is similar to the UCR, the observed drug effect. When a drug acts on the *efferent* arm of a feedback system, however, the observed drug effect is the UCS, and the CNS-mediated physiological reaction to this UCS is the UCR. Notably, in this case the UCR acts to oppose the UCS, the direct drug effect, as a result of negative feedback. The CR, like the UCR, also opposes the drug effect. Thus, CRs always mimic UCRs. Notably, this model of conditioning devised by Eikelboom and Stewart (1982) has been incorporated into models of tolerance produced by Siegel (1989) and Poulos and Cappell (1991).

Based on the model of conditioning proposed by Eikelboom and Stewart (1982), therefore, the drug-similar CRs evident in Experiment 1 are most likely due to action of morphine on the *afferent* arm of the palatability-regulating system in the CNS. In the terminology of conditioning, the taste of quinine represents the CS, while the morphine-induced modification of quinine palatability is the UCS. Consequently, both the UCR and CR are the observed attenuation in aversive responding to the taste of quinine as evident in Experiment 1. The development of conditioned drug-like responses indicates that the taste of quinine became associated with the effect of morphine on that taste. Furthermore, as few as three conditioning trials are necessary for this association to develop.

The results of this study also indicate the development of a conditioned reduction in aversion to or a conditioned taste preference for quinine. When animals repeatedly experience the effects of a drug (e.g., morphine) in the presence of a distinctive cue (e.g., quinine), they may display a modified reaction to that cue which represents a conditioned drug effect. Such conditioned drug effects have been proposed to play a role in drug tolerance (e.g., Siegel, 1978) and drug sensitization (e.g., Robinson & Berridge, 1993). The present experiment revealed evidence for neither tolerance nor sensitization, but did reveal evidence that the morphine-induced palatability shift (UCR) was conditionally elicited by the taste of quinine (CS).

The demonstration that quinine became conditionally less aversive as a result of prior pairings with the aftereffects of morphine suggests that the rats in the Contingent group developed a conditioned preference for the taste of quinine, relative

to controls in the Noncontingent group. Such a conditioned taste preference is seldom reported in the literature; in fact, when a given taste (CS) is repeatedly paired with an injection of morphine (UCS) a conditioned taste avoidance is generally reported (e.g., Riley, Jacobs & LoLordo, 1978). Recently, however, Lett and Grant (1989) have reported that under a very limited set of conditions, the pairing of a taste and morphine produces a conditioned taste preference. Studies pairing a taste with morphine have typically used a trace conditioning procedure whereby animals are exposed to the taste prior to receiving morphine. Using this procedure, Lett and Grant (1989) reported that a very low dose of morphine (0.42 mg/kg) produced a conditioned taste aversion. When rats were injected with the same dose of morphine (0.42 mg/kg) prior to a 30 min presentation of a concentrated salty or sour solution that is not naturally highly preferred, however, the rats displayed a conditioned preference for that taste in a subsequent intake test.

The present finding suggests that a similar conditioned preference (or conditioned attenuation of quinine aversiveness) can be established to quinine solution after three pairings with morphine, 30 min prior to an intraoral infusion of quinine solution. Such conditioned quinine preference is not established when an injection of morphine repeatedly follows the quinine infusion during conditioning trials (Parker, unpublished findings). Therefore, the temporal relationship between the taste and the effect of a reinforcing drug appears to be crucial to the establishment of a drug-induced conditioned taste preference as suggested by Lett and Grant (1989). Since recent investigations (e.g., Doyle et al., 1993; Rideout & Parker, unpublished

manuscript) have also demonstrated that morphine enhances the palatability of sucrose solution, it is possible that a conditioned preference for a naturally aversive quinine solution in the present study, may be established under appropriate temporal relations between the drug (UCS) and the taste (CS).

The findings of the present study have highlighted certain issues that need to be addressed in future research. First, previous research findings suggest that the development of tolerance to opiate-induced modifications of the palatability of taste stimuli may be mediated by the novelty of the tastant (Goodison & Siegel, 1992; Wolgin & Benson, 1990). Based on this rationale, it would be worthwhile to replicate the present study including a familiarization phase during which subjects would be exposed to the taste stimulus. Notably, Parker et al. (1992) did report that morphine suppresses aversive reactivity elicited by familiar as well as novel quinine, albeit to a lesser extent.

Second, given evidence of the development of a conditioned taste preference for a morphine-paired taste with the temporal design employed in this study it would be worthwhile to use this design to reassess the findings of other studies which have failed to observe the development of such a conditioned taste preference when the UCS temporally precedes the taste CS (e.g., Sherman, Pickman, Rice, Liebeskind & Holman, 1980; White, Sklar & Amit, 1977).

Finally, since this experiment has failed to demonstrate the development of tolerance to morphine-induced changes in the palatability of quinine it would be interesting to assess whether tolerance develops to the effects of an opiate antagonist

(e.g., naloxone) on the palatability of a naturally preferred tastant (e.g., sucrose). Notably, Goodison and Siegel (1992) have reported evidence of tolerance to the palatability-modifying properties of naloxone, using a simple intake measure. Since the taste reactivity test is a more direct measure of palatability it would be worthwhile to use this paradigm to investigate the development of tolerance to the effects of naloxone on the taste of sucrose using taste reactivity.

Investigations of the development of tolerance to morphine-induced modifications of the palatability of taste stimuli are worthwhile for two principal reasons. First, much of the research on the development of tolerance to the effects of morphine has focused on the analgesic response. Thus, it is interesting to consider the development of tolerance to another pharmacological property of morphine, morphine-induced modifications of palatability. Second, from an applied perspective, given the apparent ability of morphine to modify the palatability of tastants, it is clear that there is a role for endorphinergic mechanisms in consummatory behaviour; therefore, one side-effect of the recreational use of opiates may be a disturbance of the mechanisms that regulate ingestion. Therefore, from both a research and an applied perspective investigations of the development of tolerance to morphine-induced effects on the palatability of tastants are warranted.

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