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# OPPOSING EFFECTS OF INTRA-NUCLEUS ACCUMBENS MU AND KAPPA OPIOID AGONISTS ON SENSORY SPECIFIC SATIETY

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**Abstract—Mu opioid (MOP) agonists acting in the nucleus accumbens (NAcc) robustly enhance consumption of palatable foods. In addition, the effect on consumption of palatable foods produced by MOP agonists acting in the NAcc depends on both recent flavor exposure and the availability of a choice between different-flavored foods. In contrast, kappa opioid (KOP) agonists have variable effects on feeding and KOP agonists have MOP opposing behavioral actions when microinjected at several brain sites. We previously demonstrated that NAcc MOP agonists reverse the devaluation (satiety) effect of pre-feeding for a given flavor; in fact, NAcc MOP agonists selectively increase consumption of a recently sampled food. In contrast, in the present study, we found that the selective KOP agonist U50488 injected into the NAcc of rats reduced consumption of a recently sampled flavor while increasing consumption of the flavor that was not pre-fed. Intra-NAcc U50488 did not affect overall consumption or flavor preference in the absence of pre-feeding. The present data, in conjunction with our previous findings, highlight the robust and opposing role of NAcc MOP and KOP opioid receptors in palatability-based food choice and consumption and raise the possibility that an endogenous KOP agonist acting in the NAcc contributes to the phenomenon of sensory specific satiety.** 

**Key words: opioids, nucleus accumbens, feeding, palatability, choice.**

Flavor information guides decisions about food consumption that are critical for survival. In the setting of choice, the palatability of a food item (i.e. the reward value of a food, as signaled by orosensory cues (Rolls, 2001)) is essential to decision-making (e.g. what and how much of an item will be consumed), but the neural mechanisms underlying food preference are poorly understood. The opioid system is critical for the rewarding action of palatable foods. Mu opioid (MOP) receptor agonists induce robust feeding in the rat (Martin et al., 1963) by increasing the consumption of palatable food (Berridge, 1996). Accordingly, in humans, non-selective opioid antagonists reduce the positive hedonic effect of food but leave taste recognition thresholds unaffected (Yeomans and Gray, 2002).

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*Abbreviations:* DAMGO, D-Ala$^2$,N,Me-Phe$^4$,Gly-ol$^5$-enkephalin; Dyn, dynorphin; KOP, kappa opioid; MOP, mu opioid; NAcc, nucleus accumbens; SSS, sensory specific satiety.

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The nucleus accumbens (NAcc) is a critical site for opioid actions on palatability. It contains high densities of both MOP and kappa opioid (KOP) receptors as well as enkephalinergic and dynorphinergic fibers (Mansour et al., 1988; Van Bockstaele et al., 1995). Microinjection of D-Ala$^2$,N,Me-Phe$^4$,Gly-ol$^5$-enkephalin (DAMGO, a MOP receptor selective agonist) into the NAcc preferentially increases consumption of palatable items (Zhang et al., 1998; Zhang and Kelley, 2002) and preferred flavors (Woolley et al., 2006) as well as positive affective orofacial reactions to sweet tastes (Pecina and Berridge, 2005). Additionally, opioid antagonists in the NAcc selectively reduce consumption of palatable foods, indicating that endogenous opioid release modulates feeding (Segall and Margules, 1989). We have previously shown that MOP agonists within the NAcc can condition taste preferences (Woolley et al., 2007) but the effects of KOP agonists at this site are unclear. KOP antagonists in the NAcc can alter consumption under certain conditions but the range of effects differs from those of MOP antagonists (e.g. both MOP and KOP antagonists reduce deprivation and glucoprivic-induced feeding but only MOP antagonists reduce consumption of sucrose in non-deprived rats) (Bodnar et al., 1995). On the other hand, KOP agonist microinjection into the NAcc does not alter consumption of chow or a palatable sucrose solution (Majeed et al., 1986; Bakshi and Kelley, 1993; Zhang and Kelley, 1997). Furthermore, KOP agonists often have behavioral actions that are distinct from and often oppose MOP agonist actions when injected into the same brain region ((Mucha and Herz, 1985) and see (Pan, 1998) for review). To address this issue, we used a sensory specific satiety (SSS) paradigm to compare the actions of intra-NAcc MOP and KOP agonists on short term flavor conditioning and the reward value of specific tastes.

## EXPERIMENTAL PROCEDURES

### Animals

A total of 41 male rats (Long Evans, Charles River Laboratories, Wilmington, MA, USA) weighing between 270 and 450 g were used in the present studies. All procedures were approved by the UCSF Animal Care and Use Committee and conformed to international guidelines on the ethical use of animals. Every attempt was made to minimize the number of animals used and their suffering. Animals were individually housed in conventional hanging cages in a temperature- and humidity-controlled room on a 12-h light/dark cycle. Animals had *ad libitum* access to water at all times and *ad libitum* access to chow at all times except during testing.

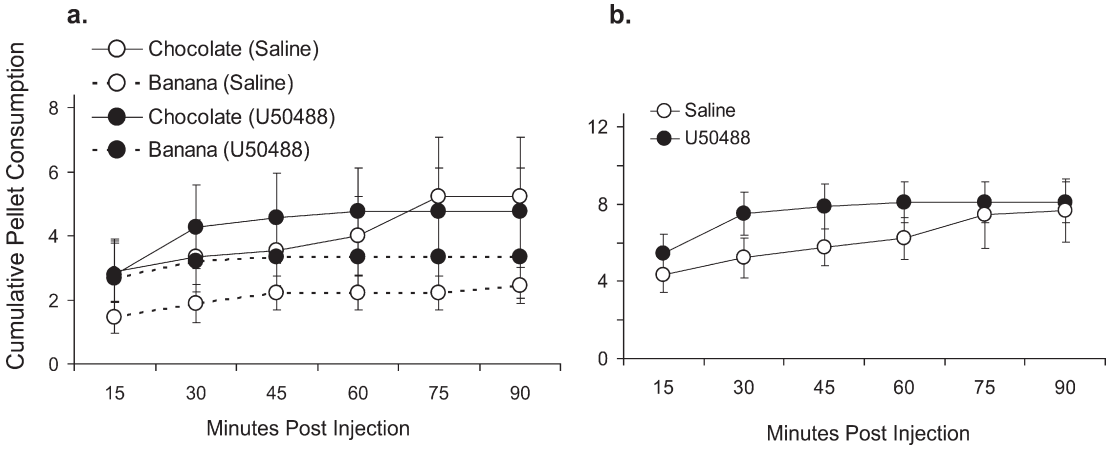


**Fig. 1.** Effect of intra-NAcc KOP receptor agonist on consumption in a choice paradigm. (a) The number of flavored pellets consumed following saline or U50488 microinjection is shown for each 15 min postinjection. Since both flavors were available after microinjection, closed circles represent data from one test session while open circles represent data from a separate test session. (b) Total cumulative consumption (chocolate plus banana) following microinjection of saline and U50488 is shown.

## Surgery

Animals were anesthetized with isoflurane, their heads placed in a stereotaxic device and then, following a small craniotomy, bilateral guide cannulae were stereotactically placed and then secured to the skull with stainless steel screws and dental cement. Coordinates for the target sites were 1.5 mm anterior, 1.1 mm lateral and 5.5 mm ventral from Bregma. For this study, the cannulae were not directed specifically at the core or the shell regions of the NAcc. For control microinjections, coordinates for the target sites were 1.5 mm anterior, 1.1 mm lateral and 3.5 mm ventral from Bregma. Animals were allowed 4 days recovery postsurgery.

## Drugs and injections

For microinjections, U50488, the selective KOP receptor agonist was obtained from Sigma Pharmaceuticals (Monticello, IA, USA). U50488 was dissolved in 0.9% sterile saline (3.25 $\mu$g per side which is equivalent to 8 nmol/$\mu$l, the highest concentration used in a previous study (Bakshi and Kelley, 1993)). First, the stylet was removed from the guide cannulae and the injector cannulae were inserted. The injector cannulae protruded 2 mm past the end of the guide cannula for a final distance of 7.5 mm ventral to Bregma. U50488, in a volume of 0.5 $\mu$l of saline, was infused through 12.5 mm injector cannulae connected to a microdrive pump by polyethylene tubing. The rate of infusion was 0.25 $\mu$l/min. The injector cannulae remained in place an additional minute after the infusion to allow for diffusion. Injectors were then removed and the stylets were replaced. For s.c. injections, U50488 was diluted in 0.9% sterile saline at a concentration of 2 mg/kg and injected s.c. with a 1 ml syringe. This concentration was chosen because it has been shown to increase consumption of palatable food in non-deprived rats (Cooper et al., 1985b).

## Behavioral testing and experimental design

After recovery from surgery (4 days), animals were extensively handled. In order to overcome taste neophobia, rats were brought into the testing room on four separate days and given 1 h simultaneous access to both flavors of pellets (chocolate and banana). After this initial exposure, all rats avidly consumed the pellets when available. The two types of flavored 1 g pellets were made from the same meal substrate and were thus matched for all macro- and micro- nutrients (Bio-Serv, Frenchtown, NJ, USA). Pellets were always delivered in test tube dispensers. Rats were required to grab the pellets with their teeth and forcibly remove them from a hole in the bottom of the tube. This amount of effort encouraged the rats to take only what they would eat and greatly facilitated consumption quantification. Every 15 min postinjection, the number of pellets remaining in the dispenser was counted and a visual inspection of the cage for dropped pellets was made. Rats were removed from their home cages for the duration of the microinjection and then immediately returned. Testing sessions were separated by at least 48 h. The SSS paradigm consisted of a pre-feeding phase that consisted of *ad libitum* access to pellets of one flavor for 1 h, an injection phase, and a post-injection test phase where rats were given simultaneous access to pellets of both flavors for 1.5 h. Before the pre-feeding phase, rats were in an *ad libitum* feeding, non-deprived state.

To determine whether intra-NAcc U50488 affects consumption in the absence of pre-feeding when rats are allowed to choose between flavors, rats ($n$=9) were microinjected with U50488 or saline into the NAcc and given 1.5 h simultaneous *ad libitum* access to both chocolate- and banana-flavored pellets. All rats underwent both conditions and injection orders were randomized.

To determine whether intra-NAcc U50488 differentially alters consumption of a flavor that has just been consumed, a SSS paradigm was used. Rats ($n$=16) were given 1 h *ad libitum* pre-feeding access to either banana or chocolate pellets. At the end of this hour, rats were microinjected with either U50488 or saline. Rats were then given 1.5 h simultaneous *ad libitum* access to both chocolate and banana flavored pellets. All rats underwent all four conditions and injection and flavor orders were randomized. As a site control, U50488 was injected 2 mm dorsal to the NAcc injection target ($n$=8). To further explore the role of NAcc KOP receptors, we repeated the same SSS paradigm but instead of injecting U50488 into the NAcc, we delivered it s.c. ($n$=18).

## Data analysis

All data are expressed as mean±S.E.M. (standard error of the mean). Data were analyzed using repeated measures ANOVA with pharmacologic manipulation, pre-feeding and flavor as repeated measures. Post hoc comparisons were made using the Bonferroni correction.

## Histology

After the completion of all testing, rats were anesthetized deeply with sodium pentobarbital and transcardially perfused with a 0.9% isotonic saline solution followed by 10% formalin solution. Brains were removed and stored in 10% formalin for several days fol-

lowed by an overnight immersion in 10% sucrose solution. Brains were cut coronally into 45 $\mu$m sections, mounted and stained with Neutral Red. Sections were examined under the microscope in order to determine placement of micro-injector tips.

## RESULTS

Similar to previous reports, in the absence of pre-feeding, U50488 microinjected into the NAcc had no significant effect on *ad libitum* consumption of either flavor (Fig. 1a, b). In contrast, in the SSS paradigm, KOP agonist microinjection in the NAcc selectively increased consumption of the flavor that had not been pre-fed. Repeated measures ANOVA indicate that U50488 significantly increased consumption [$F(1,15)=13.508$, $P<0.005$] and there was a significant drug×pre-feeding interaction [$F(1,15)=14.400$, $P<0.005$] (Fig. 2a). Post hoc mean contrasts performed on the 90 min time point indicated that U50488 significantly increased consumption of only the non-pre-fed foods ($P<0.001$) (Fig. 2c) irrespective of flavor (Fig. 2d). The significant effect of U50488 on consumption emerged by 15 min and the interaction between pre-feeding and pharmacologic manipulation became significant after 30 min of testing.

Since systemic KOP agonists generally increase consumption (Cooper et al., 1985a,b; Morley et al., 1985), we repeated the SSS paradigm with systemic U50488 injection. Systemic U50488 significantly increased consumption from the 15 min time point onward [$F(1,17)=10.456$, $P<0.01$] (Fig. 2b, d) but, in contrast to its action in the NAcc, there were no significant drug×pre-feeding or drug×flavor interactions. There was a trend for a drug×pre-feeding×flavor interaction [$F(1,17)=3.369$, $P<0.1$] that emerged at the 90 min time point. This trend was due to relatively larger U50488-induced increase in consumption of banana pellets after pre-feeding with chocolate (Fig. 2f). Taken together, these data show that U50488 increases consumption less selectively when administered systemically than when microinjected into the NAcc.

Since i.c.v. KOP agonists increase consumption, one possible confound of the U50488 NAcc injections is leakage of U50488 back along the guide cannulae into the ventricles. In order to control for this possibility, we implanted cannulae 2 mm dorsal to the NAcc microinjections. Microinjecting U50488 at this control site caused a late onset, non-selective increase in consumption. Repeated measures ANOVA on the 90 min time point indicated a significant drug effect [$F(1,7)=31.182$, $P<0.005$] (Fig. 3a) but no significant drug×pre-feeding or drug×flavor interactions (Fig. 3b). At this site, U50488 did not increase consumption until 75 min postinjection. In contrast, when microinjected into the NAcc, U50488 increased consumption significantly by 15 min. Since the control injections were closer to the ventricles, these behavioral differences rule out the possibility that U50488 is acting at other brain sites when injected into the NAcc. Finally, unlike U50488 in the NAcc, the control microinjections did not selectively increase consumption of the non-pre-fed food. Along with the systemic administration, this finding further supports the specificity of NAcc KOP receptors in enhancing SSS.

### Comparison of the effects of MOP and KOP receptor activation on consumption in a SSS paradigm

Data from our previous study (Woolley et al., 2007) of DAMGO (a MOP receptor agonist) microinjections into the NAcc using the same SSS paradigm used in the present study are shown for comparative purposes (Fig. 4a). DAMGO selectively increases consumption of the pre-fed food. Although both intra-NAcc U50488 and DAMGO increased overall consumption of food pellets following a period of pre-feeding, they had opposing effects on flavor preference when given a choice; DAMGO increases, while U50488 decreases, preference for the pre-fed flavor. In other words, intra-NAcc DAMGO significantly decreases while U50488 significantly increases SSS (Fig. 4b).

### Histology

Histological analysis showed that the injector cannulae were successfully targeted to the NAcc (Fig. 5a) and that the injector cannulae for the anatomic controls were placed in the dorsal striatum, lateral septum and ventricle (Fig. 5b).

## DISCUSSION

Pre-feeding with a given flavor reduces the palatability of that flavor and increases preference for an alternative flavor when a choice is available; so-called SSS. We previously demonstrated that intra-NAcc DAMGO reverses the SSS effect so that rats preferentially consume more of the pre-fed food (Woolley et al., 2007). In contrast, intra-NAcc microinjection of the KOP receptor agonist U50488 enhances the SSS effect of pre-feeding so that rats preferentially consume the food flavor they had not just experienced. Furthermore, in the absence of pre-feeding, unlike DAMGO, microinjection of U50488 into the NAcc had no effect on consumption. This suggests that KOP agonists in the NAcc have a selective conditioning effect on flavor preference that is opposite to that of MOP agonists.

Systemic and i.c.v. administration of KOP agonists increase (Locke et al., 1982; Cooper et al., 1985b; Morley et al., 1985; Bungo et al., 2004), and antagonists decrease (Leventhal et al., 1995; Hope et al., 1997), feeding (for review see (Cooper et al., 1985a)). Given these robust effects on consumption it is tempting to attribute them to KOP receptor–mediated actions on palatability. However, systemic KOP receptor agonists have mixed effects, increasing consumption of liquids with high sucrose concentrations and decreasing consumption of those with low concentrations (Gosnell and Majchrzak, 1989; Lynch and Burns, 1990). Additionally, i.c.v. injection of the KOP agonist U50488 failed to increase consumption of palatable saline or saccharin solutions, whereas MOP receptor agonists effectively increase consumption of these items (Gosnell et al., 1990). Because of these and other findings (Jackson and Cooper,

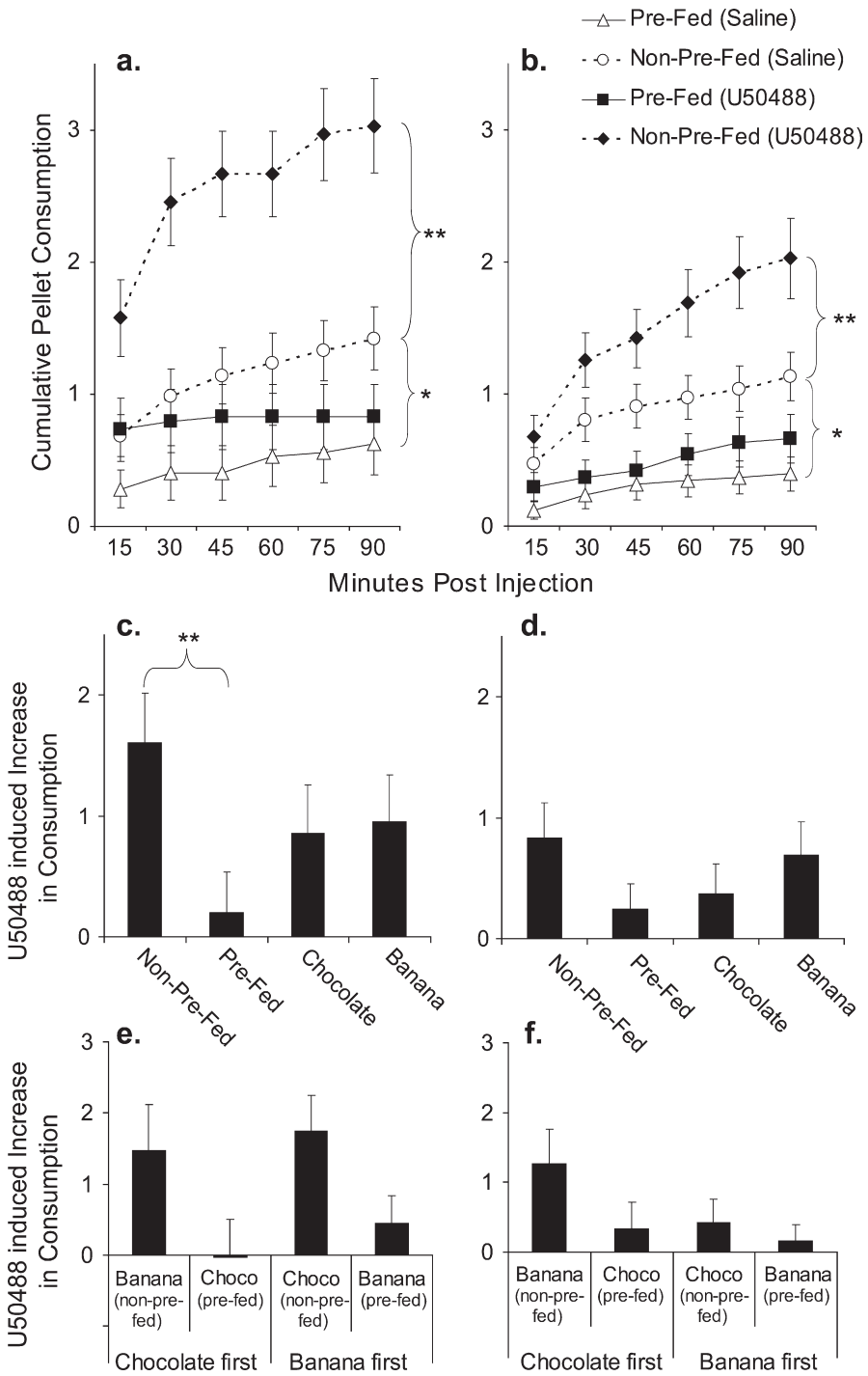


**Fig. 2.** Effects of KOP receptor agonist microinjected into the NAcc (a, c, e) or given systemically (b, d, f) on consumption in a SSS paradigm. "Pre-fed" represents the flavor which was pre-fed to the animal prior to microinjection. "Non-pre-fed" represents the flavor that was not pre-fed to the animal. (a, b) The cumulative number of pellets consumed following saline or U50488 injection into the NAcc or systemically. Data are shown for each 15 min postinjection. (c, d) U50488-induced increases in consumption are displayed for intra-NAcc microinjection (c) or systemic injection (d). Bars indicate the total number of flavored pellets consumed following U50488 minus the number consumed following saline injections at 90 min. Chocolate and banana consumption is averaged across different pre-fed and non-pre-fed conditions i.e. when chocolate is pre-fed and when banana is pre-fed. (e, f) U50488 effects displayed by which flavor is pre-fed. Bars indicate number of flavored pellets consumed at 90 min following (e) NAcc or (f) systemic U50488 injection minus the number consumed following saline injections. The two columns in the "Chocolate first" section come from trials where chocolate was the pre-fed food. The two columns in the "Banana first" section come from trials where banana was the pre-fed flavor. Labels in brackets indicate which flavor was pre-fed. * $P<0.05$, ** $P<0.01$.

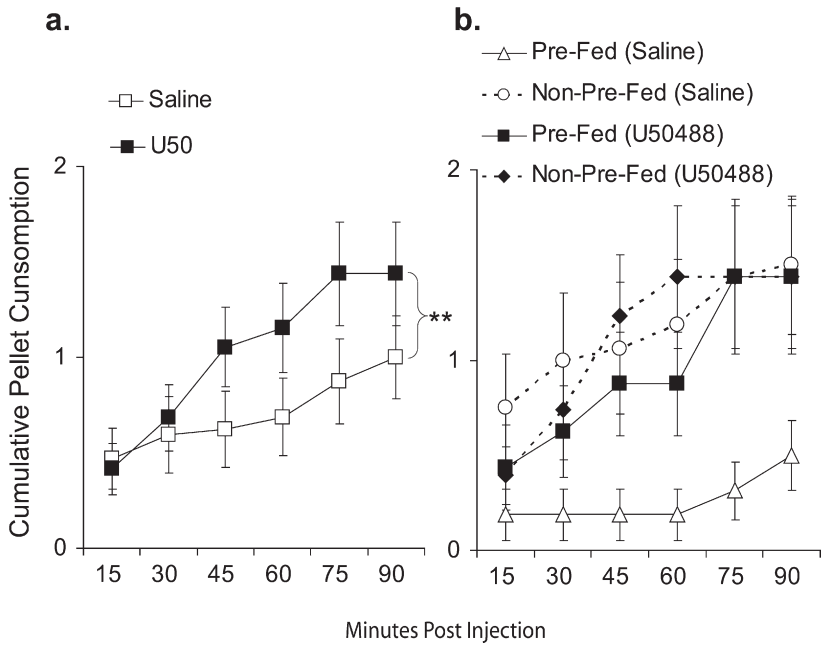


**Fig. 3.** Effect of U50488 microinjection 2 mm dorsal to NAcc microinjections on consumption in a SSS paradigm. (a) Total cumulative consumption (chocolate plus banana) following microinjection of saline and U50488 is shown. (b) The cumulative number of pellets consumed following saline or U50488 microinjection is shown for each 15 min postinjection.

1986; Badiani and Stewart, 1992, 1993; Badiani et al., 2001) systemic KOP agonists have been proposed to increase feeding by decreasing satiation (i.e. delayed meal termination), not by increasing palatability.

To further investigate the role of KOP receptors in flavor choice and to compare them with other studies using systemic administration, we repeated the SSS paradigm using systemic U50488 injections. Systemic U50488 increased consumption, but less selectively than when injected into the NAcc. This discrepancy may be due to activation of KOP receptors at sites other than the NAcc. Alternatively, although systemically administered U50488 could be acting in the NAcc; the loss of selectivity for the non-prefed flavor could be due to a delay between the experience of the flavor and KOP receptor activation. In either case, these results highlight the importance for flavor based satiety effects of the temporal proximity of activating KOP receptors in the NAcc with consumption.

Many sites where MOP agonists potently increase feeding are reportedly insensitive to KOP receptor activation. For example, intra-ventral tegmental area U50488 microinjections fail to affect feeding (Badiani et al., 1995). Dynorphin (Dyn, an endogenous KOP receptor selective agonist) injection into the nucleus of the solitary tract (Kotz et al., 1997) or the amygdala (Gosnell, 1988) also did not affect consumption of chow while DAMGO microinjections at these sites robustly increases feeding. On the other hand, Dyn microinjected into the paraventricular and ventromedial hypothalamic nuclei, but not the globus pallidus, striatum or lateral hypothalamus, did increase intake of chow (Gosnell et al., 1986; Gosnell, 1988). Furthermore, lesions of the globus pallidus and striatum attenuate systemic ketocyclazocine (a KOP receptor agonist) -induced feeding (Gosnell et al., 1984) suggesting that these sites are important for KOP receptor–mediated feeding. Perhaps the globus pallidus and striatum are necessary downstream nodes in the feeding circuit (Will et al., 2003).

We found that intra-NAcc U50488 increases consumption in a flavor choice paradigm but only when rats have been pre-fed one of the alternative flavors. The lack of U50488 effects in the absence of pre-feeding is in agreement with previous studies showing intra-NAcc KOP receptor agonists generally fail to increase consumption (Majeed et al., 1986; Bakshi and Kelley, 1993; Kelley et al., 1996; Zhang and Kelley, 1997). For example, U50488 and bremazocine (a KOP receptor agonist) microinjected into the NAcc were completely ineffective (Majeed et al., 1986; Bakshi and Kelley, 1993) while Dyn only increased consumption of bland chow at high concentrations (10 nmol) (Majeed et al., 1986). Importantly, neither intra-NAcc U50488 nor Dyn altered consumption of a sucrose solution (Zhang and Kelley, 1997). Intra-NAcc nor-binaltorphimine (a KOP receptor antagonist) also failed to change consumption of chow in food-deprived animals or sucrose in non-deprived animals (Kelley et al., 1996). These results suggest that behavioral context (i.e. the availability of alternative flavors in a choice paradigm), recent flavor experience and flavor of the available food are critical parameters that determine the sign of opioidergic effects. In particular, it appears that a flavor must be temporally contiguous with KOP agonist action in the NAcc in order for the KOP agonist to enhance consumption of the alternative flavor.

We compared the results of the present study to those of our previous study on the effects of MOP receptor agonists in the NAcc (Woolley et al., 2007) on the grounds

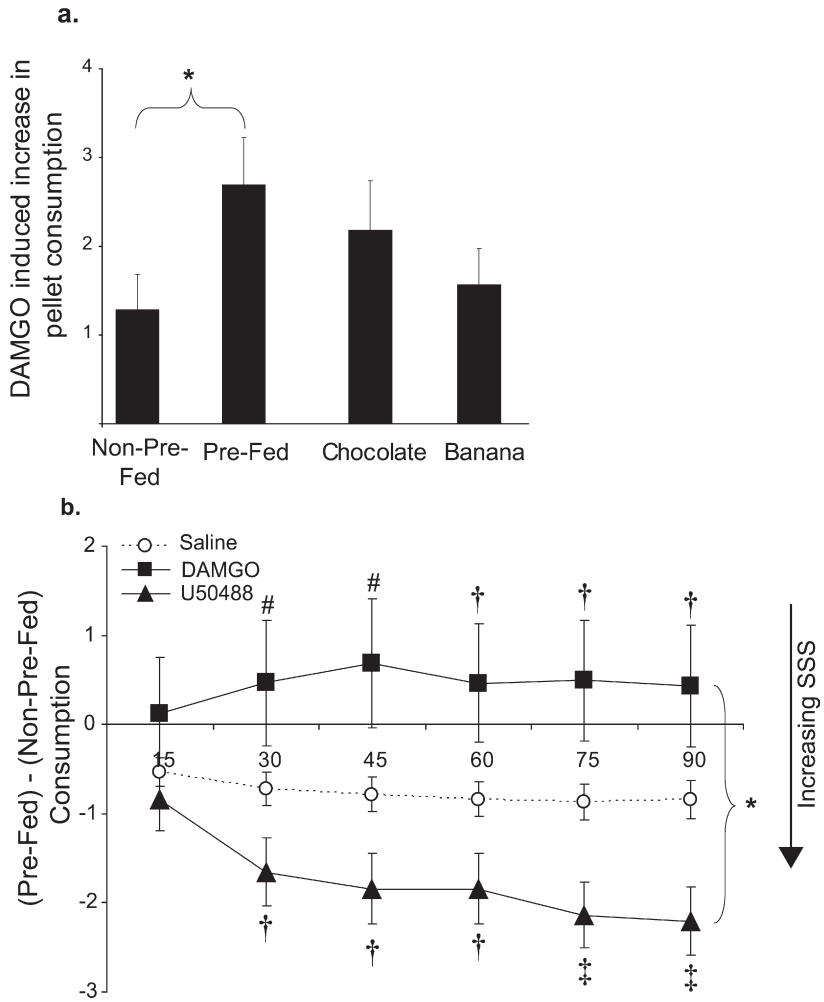


**Fig. 4.** Effects of MOP (data published previously, Woolley et al., 2007) and KOP receptor agonists in a SSS paradigm. (a) DAMGO induced increases in consumption. Bars indicate the total number of flavored pellets consumed following DAMGO minus the number consumed following saline microinjections at 90 min. Chocolate and banana consumption is averaged across different pre-fed and non-pre-fed conditions i.e. when chocolate is pre-fed and when banana is pre-fed. (b) DAMGO decreases while U50488 increases the magnitude of SSS. The difference between pre-fed and non-pre-fed consumption is shown for DAMGO, U50488 and saline. A negative value denotes greater relative consumption of the non-pre-fed food. ‡ $P<0.005$, † $P<0.01$, # $P<0.05$ all compared with saline.

that both studies used identical behavioral paradigms, surgical techniques and microinjection procedures. By combining these data, we found opposing effects of intra-NAcc MOP and KOP receptor agonists. This is consistent with previous studies showing opposing roles of these opioid receptor subtypes in multiple paradigms. For example, intra-VTA MOP agonists produce positive taste reinforcement (Mucha and Herz, 1985) and conditioned place preference; rats spend more time in a context paired with MOP agonist administration than in a saline-paired environment (Phillips and LePiane, 1980; Bals-Kubik et al., 1993; Nader and van der Kooy, 1997). Conversely, intra-VTA microinjections of KOP agonists produce conditioned taste (Mucha and Herz, 1985) and place aversion (Bals-Kubik et al., 1993). Similarly, in the NAcc, MOP agonists promote, while KOP agonists antagonize, capsaicin-induced antinociception and KOP receptor agonists completely block the ability of MOP agonists to promote antinociception (Schmidt et al., 2002).

## CONCLUSION

In conclusion, our previous work has shown that the MOP receptor selective agonist DAMGO in the NAcc enhances the reward value (i.e. produces positive reinforcement of consumption) of the immediately preceding flavor; enhancing preference for and consumption of it relative to other tastes. In contrast, the KOP agonist U50488 in the NAcc, reduces the preference for the just-experienced flavor, thus enhancing SSS as measured by increased consumption of the relatively novel alternative flavor. Furthermore, as reported by others and unlike its effects in the SSS paradigm, intra-NAcc U50488 has no effect on overall consumption or flavor preference in the absence of pre-

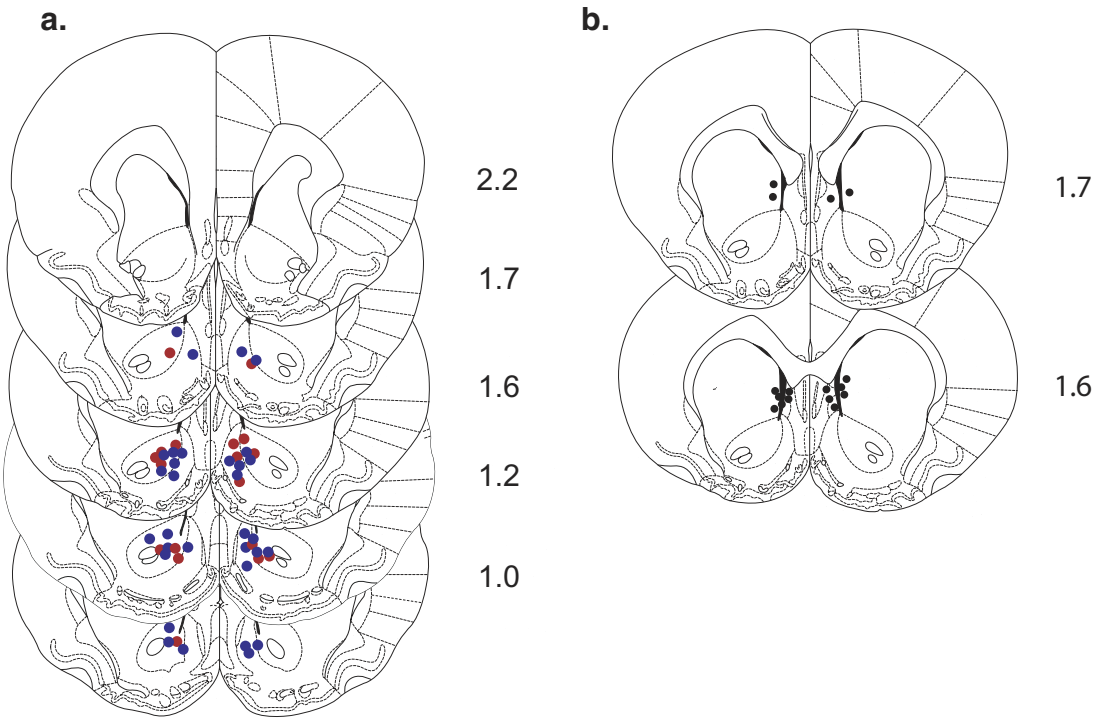


**Fig. 5.** Cannulae placements in the NAcc. (a) Red circles denote cannulae placements in rats microinjected with U50488 in the choice paradigm. Blue circles denote cannulae placements in rats microinjected with U50488 in the SSS paradigm. (b) Black circles denote cannulae placements in rats microinjected with U50488 2 mm dorsal to our previous microinjections. Numbers denote millimeters anterior to Bregma.

feeding. These findings point to a novel opposing role of MOP and KOP receptors within the NAcc on flavor conditioning and taste preference.

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