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Research report

A systematic investigation of the differential roles for ventral tegmentum serotonin 1- and 2-type receptors on food intake in the rat

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ABSTRACT

Central serotonin (5-HT) pathways are known to influence feeding and other ingestive behaviors. Although the ventral tegmentum is important for promoting the seeking and consumption of food and drugs of abuse, the roles of 5-HT receptor subtypes in this region on food intake have yet to be comprehensively examined. In these experiments, food restricted rats were given 2-h access to rat chow; separate groups of non-restricted animals had similar access to a sweetened fat diet. Feeding and locomotor activity were monitored following ventral tegmentum stimulation or blockade of 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C} receptors. 5-HT_{1A} receptor stimulation transiently inhibited rearing behavior and chow intake in food-restricted rats, and had a biphasic effect on non-restricted rats offered the palatable diet. 5-HT_{1B} receptor agonism transiently inhibited feeding in restricted animals, but did not affect intake of non-restricted rats. In contrast, 5-HT_{1B} receptor antagonism decreased palatable feeding. Although stimulation of ventral tegmental 5-HT_{2B} receptors with BW723C86 did not affect hunger-driven food intake, it significantly affected palatable feeding, with a trend for an increasing intake at 2.0 μg/side but not at 5.0 μg/side. Antagonism of the same receptor modestly but significantly inhibited feeding of the palatable diet at 5.0 μg/side ketanserin. Neither stimulation nor blockade of 5-HT_{2A} or 5-HT_{2C} receptors caused prolonged effects on intake or locomotion. These data suggest that serotonin's effects on feeding within the ventral tegmentum depend upon the specific receptor targeted, as well as whether intake is motivated by food restriction or the palatable nature of the offered diet.

1. Introduction

Of the many attempts to develop pharmacological tools for weight loss, those drugs that impact central serotonin (5-HT) signaling have had the most success to date. Indeed, two of the three current FDA-approved agents for assisting long-term efforts at dieting (the phentermine/topiramate combination, Qsymia® and lorcaserin, Belviq®) both affect serotonergic mechanisms. Phentermine generally increases 5-HT tone in the synapse, whereas lorcaserin is a selective agonist that acts upon the 5-HT_{2C} receptor. There are over 14 individual subclasses of 5-HT receptors, and given the modest successes of lorcaserin, there is hope that selective agonists/antagonists at individual receptors may assist with weight loss without causing the cardiovascular side effects that have resulted in the market withdrawal of some previous serotonin-based pharmacotherapies, such as the phentermine/fenfluramine combination that was prescribed briefly in the late 1990s (fen-phen) and the more recently withdrawn sibutramine.

Although serotonin is found both peripherally and within the central nervous system, it is generally accepted that its actions in regulating meal size and satiety are accomplished within the brain. Particular attention has been paid to the roles of serotonin signaling in the brain stem, which receives input from the tongue and the gut, as well as the hypothalamus, which promotes food-seeking and intake based upon the current energy state of the organism (for reviews, see Lenard and Berthoud, 2008; Simansky, 1996; Woods and D'Alessio, 2008). Specific 5-HT receptor subtypes in both regions have been implicated in regulating food intake and satiety processes. For instance, 5-HT_{1B} receptors in the parabrachial nucleus of the pons inhibit feeding (Lee et al., 1998; Simansky and Nicklous, 2002), and 5-HT_3 receptors of the nucleus of the solitary tract mediate CCK-induced reductions of feeding (Hayes and Covasa, 2006a, 2006b). In the hypothalamus, 5-HT_{2C} receptor activation reduces food intake, likely by affecting melanocortin signaling (Heisler et al., 2003; Lam et al., 2008; López-Alonso et al., 2007; Zhou et al., 2005). These data suggest that

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serotonin signaling is an important modulator of food motivation across multiple levels of the nervous system.

Thus far, examination of the potential regulation of serotonin systems on feeding has largely neglected its impact on circuits of the brain that process the reinforcing and hedonic aspects of food. This is striking because it has been argued that the current rise in the obesity epidemic may largely be due to heightened availability and consumption of cheap, hyperpalatable, and energy-rich foods that promote intake beyond energy needs (i.e., Berridge et al., 2010; Berthoud et al., 2011; Kelley et al., 2005; Stice et al., 2013). Recent research suggests that serotonin can also regulate food intake and motivation through action in forebrain regions, including the prefrontal cortex (Mena et al., 2011; Stanquini et al., 2015) and the nucleus accumbens (Clissold et al., 2013; Francis et al., 2011; Jean et al., 2007; Pratt et al., 2009). Our laboratory and others have investigated the role of a subset of 5-HT receptors of the nucleus accumbens on food intake and motivation. The examination thus far suggests that stimulation of 5-HT_{1A} and 5-HT_4 receptors of the anterior nucleus accumbens shell inhibit food intake, whereas stimulation of the 5-HT_6 receptor increases feeding. Furthermore, nucleus accumbens 5-HT_{1A} and 5-HT_6 receptor stimulation decreases and increases motivation, respectively, in a progressive ratio task where rats work to earn sugar pellets (Pratt et al., 2012). These findings suggest that serotonin, in addition to modulating brain stem and hypothalamic homeostatic circuitry, may regulate food motivation by directly impacting brain reward pathways.

The ventral tegmental area (VTA) is heavily interconnected with the hypothalamus and the nucleus accumbens (Oades and Halliday, 1987), and has been shown to be critically involved in promoting the intake of drugs of abuse as well as food. For instance, pharmacological manipulations of dopaminergic and opioid neurotransmission within the VTA impact food intake and motivation (e.g., MacDonald et al., 2004, 2003; Mucha and Iversen, 1986; Noel and Wise, 1995; Sharf et al., 2005). However, there has been no systematic investigation of the role of individual 5-HT receptor subtypes of the ventral tegmentum on feeding. As part of a broader effort to understand the potential modulatory roles of meso-accumbens 5-HT receptor signaling on food intake and motivation, here we examined the impact of pharmacological stimulation or blockade of ventral tegmentum 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors on rats' food intake in response to energy need or to the presence of a palatable sweetened fat diet.

2. Results

2.1. VTA 5-HT_{1A} stimulation and blockade on hunger- and palatability-driven feeding

In food restricted animals offered rat chow, stimulation of 5-HT_{1A} receptors of the ventral tegmentum with 8-OH-DPAT yielded a significant effect of drug ($F_{3,15}=4.02$, $p=.028$) and a significant drug X time interaction effect ($F_{69,345}=3.42$, $p<.001$). As can be seen in Fig. 1, 5-HT_{1A} receptor stimulation caused a dose-dependent inhibition of feeding within the first hour of the feeding session. Follow-up ANOVAs at individual time points yielded significant differences between drug doses for all points examined within the first hour. Even when rats received the highest dose of 8-OH-DPAT, their feeding caught up to baseline levels during the second hour of testing. There was no significant effect of drug on ambulation as measured by cage crossings ($F_{3,15}=2.33$, $p=.116$) nor water intake ($F_{3,15}=.94$, $p=.445$), although the 8.0 μg dose of the 8-OH-DPAT significantly reduced rearing behavior across the session (drug effect: $F_{3,15}=11.44$, $p=.02$; Tukey's HSD pairwise comparisons $p<.05$).

Though consumption of the palatable diet was more variable than that of rat chow in food restricted animals, stimulation of the 5-HT_{1A} receptors also affected intake of the sweetened fat diet. There was a significant effect of drug ($F_{3,18}=4.36$, $p=.018$), as well as a significant drug X time interaction effect ($F_{69,414}=1.58$, $p=.004$). As can be seen in the bottom panels of Fig. 1, rats that received the highest dose of drug ate the least amount of food across the session. Significant differences between drug treatments were apparent by 15 min into the session, although Tukey's HSD analyses at 5-min intervals suggest that the difference between the 2.0 μg and 8.0 μg drug treatments was primarily responsible for this effect, as neither dose was significantly different from vehicle treatment at the time points tested. This suggests that under these testing conditions, there was a biphasic impact of 5-HT_{1A} receptor stimulation on palatable feeding. Furthermore, there were significant effects of drug treatment on ambulation ($F_{3,18}=3.21$, $p=.048$), although post-hoc analysis did not determine a significant difference of any of the drug conditions from the vehicle injection day. There were no effects on rearing ($F_{3,18}=1.14$, $p=.358$), nor was there a significant effect of drug on water intake ($F_{3,18}=2.73$, $p=.075$).

Despite the effects of ventral tegmental 5-HT_{1A} receptor stimulation on food intake in both the food-restricted and palatable-feeding groups, blockade of the same receptor with WAY 100635 did not significantly change food intake or locomotor measures. There was no significant effect of drug dose ($F_{3,12}=2.30$, $p=.129$), nor a drug X time interaction ($F_{69,276}=1.32$, $p=.062$), on intake of rat chow in hungry rats. Neither did hungry animals exhibit significant changes in ambulation ($F_{3,15}=.19$, $p=.905$), rearing behavior ($F_{3,15}=1.85$, $p=.182$) or water intake ($F_{3,15}=2.02$, $p=.155$) across the drug doses tested. There were also no effects of ventral tegmental antagonism of 5-HT_{1A} receptors on palatable intake in non-restricted rats (drug effect: $F_{3,24}=.49$, $p=.689$; drug X time interaction: $F_{69,552}=.443$, $p=.999$). Ambulation, rearing, and water intake were also unaffected by drug treatment (all p's $>.1$).

2.2. VTA 5-HT_{1B} stimulation and blockade on hunger- and palatability-driven feeding

In food-restricted animals offered rat chow, stimulation of 5-HT_{1B} receptors of the ventral tegmentum yielded a significant interaction of drug × time ($F_{69,345}=1.65$, $p=.002$), though there was not a significant main effect of the drug ($F_{3,15}=1.51$, $p=.253$). As can be seen in Fig. 2, drug treatment slowed initial feeding. Both the 2.0 and 4.0 μg/side doses of the 5-HT_{1B} agonist CP 93129 caused significantly less feeding in the first five minutes compared to vehicle injections, and this difference was sustained for the first 25 min of the session for the 4.0 μg/side condition. Though there was a trend for the drug to also inhibit feeding during the middle of the second hour, there were no significant differences between the vehicle condition and any drug dose when examined at the individual time points (all ANOVA p's $>.05$). Certainly, by the end of the second hour, rats had eaten equivalent amounts of food across all treatment conditions ($F_{3,15}=.73$, $p=.552$, as assessed at 2 h). Although there was a tendency for the rats to rear less after receiving the high dose of drug, neither rearing ($F_{3,15}=2.21$, $p=.129$), ambulation ($F_{3,15}=.93$, $p=.924$), nor water intake ($F_{3,15}=.04$, $p=.988$) significantly differed across drug treatments in food-deprived rats. Blockade of the receptor had no effect on food intake or locomotion; a separate set of rats, tested with ventral tegmentum injections of the 5-HT_{1B} antagonist GR 55562, showed no effects on food intake (drug effect: $F_{3,21}=1.82$, $p=.174$; drug × time interaction: $F=.04$, $p=.988$), ambulation ($F_{3,21}=.012$, $p=.949$), rearing ($F_{3,21}=.606$, $p=.618$), or water intake ($F_{3,21}=.652$, $p=.590$).

These effects contrast with the impact of the same agents in ad libitum-fed animals that were offered a sweetened fat diet. In