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Activation of oxytocin receptors, but not arginine-vasopressin V1a receptors, in the ventral tegmental area of male Syrian hamsters is essential for the reward-like properties of social interactions

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ABSTRACT

Social reward plays a fundamental role in shaping human and animal behavior. The rewarding nature of many forms of social behavior including sexual behavior, parental behavior, and social play has been revealed using well-established procedures such as the conditioned place preference test. Many motivated social behaviors are regulated by the nonapeptides oxytocin (OT) and arginine vasopressin (AVP) through their actions in multiple brain structures. Interestingly, there are few data on whether OT or AVP might contribute to the rewarding properties of social interaction by their actions within brain structures that play a key role in reward mechanisms such as the ventral tegmental area (VTA). The goal of the present study was to investigate the role of OT and AVP in the VTA in regulating the reward-like properties of social interactions. Social interactions between two male hamsters reduced a spontaneous place avoidance in hamsters injected with saline control. Interestingly, however, OT and AVP injected into the VTA induced a significant two-fold reduction in place avoidance for the social interaction chamber when compared to control injections of vehicle. Finally, because OT and AVP can act on each other's receptors to influence social behavior, we also injected highly selective OTR and V1aR agonists and antagonists to determine whether OT or AVP V1a receptors were responsible for mediating the effects of these neuropeptides on social reward. Our results not only demonstrated that OT and AVP activate OTRs and not V1aRs to mediate social reward, they also demonstrated that the activation of OT receptors in the VTA is essential for the expression of the rewarding properties of social interactions.

1. Introduction

The fact that many forms of social interaction have rewarding properties plays fundamental role in human and animal behavior. Indeed, the frequency with which groups of humans gather together illustrates the powerful rewarding properties of social interactions (Wagner et al., 2015). The neural mechanisms underlying social reward have been studied in a variety of species ranging from those that live in large social groups like rats to those that are less socially gregarious like Syrian hamsters (Mattson and Morrell, 2005; Meisel et al., 1996; Peartree et al., 2012; Trezza et al., 2011). The power of social reward is illustrated by the findings even in less gregarious species like hamsters that social interactions are not only rewarding for individuals that win competitive interactions, but also for those that lose as long as the loss is not too severe (Gil et al., 2013; Huhman, 2006). Indeed, social reward, along with social skills such as social recognition and social communication play a critical role in the development of adaptive social relationships in all mammalian species. The rewarding nature of social interactions even in species such as hamsters result in their ability to establish enduring social organizations including hierarchical dominant/subordinate relationships (Albers et al., 2002; Drickamer and Vandenbergh, 1973; Drickamer et al., 1973). Defining the mechanisms underlying social reward is not only critical for understanding the expression of adaptive social behavior, but also

Abbreviations: AH, anterior hypothalamus; AVP, arginine vasopressin; BNST, the bed nucleus of the stria terminalis; CPP, conditioned place preference; DA, dopamine; LS, lateral septum; MPOA, medial preoptic area; NAcc, nucleus accumbens; OTR, oxytocin receptor; OT, oxytocin; PAG, periaqueductal gray; SBNN, social behavior neural network; V1aR, vasopressin 1a receptor; VMH, ventromedial nucleus of the hypothalamus; VTA, ventral tegmental area.

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for revealing the dysfunctions in these mechanisms that contribute to the development of psychiatric disorders (Bora et al., 2009).

Oxytocin (OT) and arginine-vasopressin (AVP) are evolutionarily conserved mammalian neuropeptides that play essential roles in regulating a variety of motivated social behaviors including aggression, social recognition, parental behavior and social communication (Albers, 2012; Caldwell et al., 2008; Dumais and Veenema, 2015; Hammock, 2015; Ishak et al., 2011; Kelly and Goodson, 2014). The central effects of OT and AVP on social behavior are mediated primarily through the activation of OT receptors or AVP V1a receptors (Albers et al., 1986; Insel, 1992) as the expression of V1b receptors is restricted in the brain (Dhakar et al., 2013) and V2 receptors are not centrally expressed (Barberis et al., 1998). Many of the behavioral effects of OT and AVP are the result of their actions in structures that have been proposed to form a social behavior neural network (SBNN) (Newman, 1999). There is increasing evidence that the SBNN, composed of neural groups or "nodes" including, but not limited to, the extended amygdala, the bed nucleus of the stria terminalis (BNST), lateral septum (LS), periaqueductal gray (PAG), medial preoptic area (MPOA), ventromedial hypothalamus (VMH), and anterior hypothalamus (AH), plays a critical role in the expression of many different social behaviors (Albers, 2015; Crews, 1997; Goodson and Kingsbury, 2013).

It is likely that the expression of motivated social behaviors, like other motivated behaviors, also requires the activity of the mesolimbic dopamine (DA) system. The mesolimbic DA system is a network of reciprocally connected brain regions that are involved in determining the salience of stimuli, assigning their hedonic value, and initiating appropriate action (Caldwell and Albers, 2016; Love, 2014). There is also evidence that the mesolimbic DA system can play a critical role in at least some forms of social behavior (Aragona et al., 2003, 2006; Aragona and Wang, 2009; Curtis and Wang, 2005). While the SBNN and the mesolimbic DA system are distinct from one another, it has been proposed that they cooperate in the process of social decision making (O'Connell and Hofmann, 2011a,b). The mechanisms underlying the cooperation between these systems are not known but likely involve the actions of OT and AVP within the mesolimbic DA system.

The VTA is a key region in the mesolimbic DA system and provides many of the dopamine containing projections that innervate cortical and limbic structures that form the circuitry underlying motivation. The purpose of the present study was to test the hypothesis that activation of OT and/or V1a receptors in the VTA mediates the reward-like properties of social interaction in male Syrian hamsters. Because OT and AVP can influence social behavior by acting on each other's receptors (Sala et al., 2011; Song et al., 2014) we also determined which receptors are responsible for inducing social reward by applying highly selective OT and AVP receptor agonists and antagonists.

2. Materials and methods

2.1. Animals

Adult male Syrian hamsters (*Mesocricetus auratus*), purchased from Charles River Laboratories Inc., Wilmington, MA, USA, were used in all experiments. The experimental hamsters were 10–12 weeks old, weighed 110–130 g, and were singly housed in polycarbonate cages (23 × 43 × 20 cm) upon arrival to our vivarium. The stimulus hamsters were 8–10 weeks old, weighed 90–100 g, and were housed in a group of 4 per cage upon arrival. All hamsters were kept on a 14:10 light/dark cycle with food and water *ad libitum*. All experimental procedures were in accordance with the National Institutes of Health Guidelines for the Use of Animals and were approved by the Georgia State University Animal Care and Use Committee.

2.2. Surgery, and microinjections

2.2.1. Surgery

Seven days after arrival, hamsters were anesthetized with 5% isoflurane in an induction chamber and maintained with 3.75% isoflurane throughout all surgical procedures. A 4 mm, 26-gauge cannula guide was implanted unilaterally in each experimental hamster aimed at the VTA (−2.9 mm anterior to bregma, −0.6 mm from the midline, and −2.9 mm below dura) producing injection sites close to the midline. The guide was affixed to the skull using wound clips and Ortho-Jet dental acrylic (Lang Dental, Wheeling, IL, USA). Ketefen (1 ml/kg) was injected I.P. for analgesia and hamsters were monitored daily for 3 days and given additional ketefen as required.

2.2.2. Microinjections

Hamsters were gently restrained and microinjections were given over the course of 1 min using an infusion pump (Harvard Apparatus), a 1 μl Hamilton syringe, and a 12 mm, 32-gauge microinjection needle. The volume of all microinjections was 250nl. Following the injection, the needle was left in the cannula guide for an additional minute to allow drug diffusion into the VTA. At the end of the experiment experimental hamsters were sacrificed by lethal injection of sodium pentobarbital (2 ml/kg) and were injected with 250nl ink to mark the injection sites (see cannula placements in Fig. 1).

2.3. Drugs

The following drugs were used: 9 μM, 90 μM OT (Bachem, CA, USA) and AVP (Fisher scientific, TX, USA); 27 μM [Thr4,Gly7]OT (OTAG, a highly selective OT receptor agonist (Lowbridge et al., 1977), a gift of Dr. Maurice Manning); 0.23 μM and 23 μM [Phe2]OVT (V1aAG, a highly selective V1a receptor agonist (Huguenin, 1964; Manning et al., 2012), a gift of Dr. Maurice Manning); 90 μM desGly-NH2-d(CH2)5[D-Tyr2,Thr4]OVT (OTA, a selective OTR antagonist (Manning et al., 1995), a gift of Dr. Maurice Manning) and 90 μM d(CH2)5[Tyr(Me)2]AVP (V1aA, a selective V1aR antagonist known as Manning Compound (Kruszynski et al., 1980), a gift of Dr. Maurice Manning). The concentrations of OT and AVP administered were based on the concentrations used in previous studies that were found effective in altering other social behavior in hamsters (Albers et al., 2006; Harmon et al., 2002; Song et al., 2014). The concentrations of the OT and AVP agonists used in these experiments (*i.e.*, OT agonist: 27 μM [Thr4,Gly7]OT and V1a agonist: 0.23 μM [Phe2]OVT) were chosen based on dose-response studies of their efficacy in inducing social communication behavior in Syrian hamsters (Song et al., 2014) and their relative efficacies compared to OT and AVP in binding to OTR and V1aR in rats (Manning et al., 2012). The concentration of both OTR and V1aR antagonists were based on the concentration established in previous studies that was found to block social behavior in hamsters and rats (Albers et al., 1986; Nephew and Bridges, 2008). All controls were given a 250 nl injection of saline.

2.4. Behavioral testing

Male hamsters were tested using conditioned place preference (CPP) to examine whether social interaction with another male adult hamster could induce conditioned place preference, and if so, how much change in chamber preference would be induced by social interaction. Drugs of interest and saline were