



Regular article

Adolescent exposure to oxytocin, but not the selective oxytocin receptor agonist TGOT, increases social behavior and plasma oxytocin in adulthood



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ABSTRACT

There are indications that exposing adolescent rodents to oxytocin (OT) may have positive “trait-changing” effects resulting in increased sociability and decreased anxiety that last well beyond acute drug exposure and into adulthood. Such findings may have relevance to the utility of OT in producing sustained beneficial effects in human psychiatric conditions. The present study further examined these effects using an intermittent regime of OT exposure in adolescence, and using Long Evans rats, that are generally more sensitive to the acute prosocial effects of OT. As OT has substantial affinity for the vasopressin V1a receptor (V1aR) in addition to the oxytocin receptor (OTR), we examined whether a more selective peptidergic OTR agonist – [Thr4, Gly7]-oxytocin (TGOT) – would have similar lasting effects on behavior. Male Long Evans rats received OT or TGOT (0.5–1 mg/kg, intraperitoneal), once every three days, for a total of 10 doses during adolescence (postnatal day (PND) 28–55). Social and anxiety-related behaviors were assessed during acute administration as well as later in adulthood (from PND 70 onwards). OT produced greater acute behavioral effects than TGOT, including an inhibition of social play and reduced rearing, most likely reflecting primary sedative effects. In adulthood, OT but not TGOT pretreated rats displayed lasting increases in social interaction, accompanied by an enduring increase in plasma OT. These findings confirm lasting behavioral and neuroendocrine effects of adolescent OT exposure. However, the absence of such effects with TGOT suggests possible involvement of the V1aR as well as the OTR in this example of developmental neuroplasticity.

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Introduction

A fundamental characteristic of humans and other mammals is a strong innate desire for social contact. Whether fleeting or enduring, social experiences have a complex capacity to influence our physical and psychological wellbeing (Neumann, 2009). While the regulation of social behavior involves multiple complex inputs, the neuropeptides oxytocin (OT) and vasopressin (AVP) appear to have key roles.

In general terms, OT appears to modulate the salience of social stimuli to facilitate social approach (Young, 2011). Indeed, oxytocin receptor (OTR) null mice (OTR^{−/−}) lack the natural preference for social over non-social stimuli (Sala et al., 2011), while rodents pretreated with an OTR antagonist also show reduced social preference (Lukas et al., 2011). In tests of social interaction, chronic intracerebroventricular (ICV) OT in male rats increases the amount of time spent in direct physical contact with other rats in the absence of any changes in sexual behavior, locomotor activity, or core body temperature (Witt et al.,

1992). OT also rescues normal social preference in rats made socially “phobic” via a social defeat experience (Lukas et al., 2011). Moreover, peripherally administered OT or AVP given to male Long Evans rats meeting for the first time, increased the amount of time spent in ‘adjacent lying’, a prosocial behavior during which two rats lie passively next to each other for prolonged periods (Ramos et al., 2013).

There is additional interest in the longer lasting residual effects of OT treatment on social behavior. Our group recently discovered that daily injections of OT (1 mg/kg, intraperitoneal (IP)) for ten days during early adolescence in rats lead to subsequent decreases in anxiety-like behavior and significant increases in sociability during adulthood (Bowen et al., 2011). These lasting social changes were accompanied by significant up-regulation of OTR mRNA in hypothalamic tissue and a trend towards increased plasma OT (Bowen et al., 2011). Such findings are consistent with physiological studies suggesting profound plasticity in hypothalamic OT systems, and a feedforward capacity whereby exogenous OT stimulation promotes endogenous OT release and hypertrophy of OT magnocellular neurons (Theodosios, 2002; Theodosios et al., 1986). These observations also agree with earlier work where chronic OT administration fostered a ‘behaviorally calm’ anti-stress state characterized by a lasting reduction in blood pressure and plasma corticosterone (Petersson et al., 1997, 1999).

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The present study further examined the effects of adolescent OT exposure on subsequent behavior in adulthood. Of specific interest was a comparison of the effects of OT with those of a more selective OTR agonist, the peptide analog of OT called [Thr4, Gly7]-oxytocin (TGOT). OT has relatively low selectivity for the OTR over AVP receptor subtypes, particularly the vasopressin 1A receptor, V1aR (Brida et al., 2012; Hicks et al., 2012; Terrillon et al., 2002). Thus it is feasible that OT acts at the V1aR to mediate some of its key behavioral effects (Busnelli et al., 2013; Ramos et al., 2013). For example, Sala et al. (2011) showed that OT and AVP administered ICV rescued the abnormal social exploration and social recognition of OTR^{−/−} mice via an action on V1a receptors. TGOT is fundamentally similar to OT, but has very low affinity for the rat V1aR (>10,000 nM) and V1bR (8000 nM) relative to the OTR (0.8 nM) (Manning et al., 2012). TGOT thus permits the study of OTR-related effects with greater specificity than with OT itself which has affinities of 71.0 nM (rat V1aR), 294 (rat V1bR) and 1.0 nM (rat OTR) (Manning et al., 2012).

The acute behavioral effects of TGOT in rodents are not well characterized, particularly when administered peripherally. In a recent study, delivery of equivalent ICV doses of TGOT or OT rescued the social deficits seen in knockout mice heterozygous for the OTR gene (OTR^{+/-}), suggesting dose equivalence in acute behavioral effects (Sala et al., 2012). Here we administered equivalent peripheral doses of TGOT and OT in adolescence and examined acute behavioral effects in models of social behavior and anxiety, as well as then examining any lasting residual effects in adulthood. Long Evans rats were used rather than the Albino-Wistar rats used in our earlier studies (Bowen et al., 2011; Hicks et al., 2012), given the high sensitivity of this strain to the prosocial effects of OT and AVP (Ramos et al., 2013).

The style of social interaction between adolescent and adult rats is qualitatively different (Spear, 2000). Social play behavior, characterized by 'rough-and-tumble' play, displays an inverted U-shaped curve across development, peaking in mid-adolescence at post-natal day (PND) 30 and disappearing in early adulthood at PND 60 (Pellis & Pellis, 2007; Trezza & Vanderschuren, 2008). During this period, robust reorganization in V1a and OT receptor expression is observed within several brain regions and is likely to be associated with the development adult-typical social behaviors (Lukas et al., 2010; Veenema et al., 2013). Thus by examining behavioral effects in adolescent rats that were acutely dosed with OT and TGOT we are able to discern, for the first time, the dose-dependent effects of OT and TGOT on social play.

In assessing lasting residual behavioral changes in adulthood resulting from OT and TGOT exposure, both social and anxiety-related behaviors were targeted. An additional interest was any persistent endocrine changes following repeated peripheral OT and TGOT that might underlie any observed changes in behavior. It was hypothesized that repeated adolescent exposure to OT, and perhaps TGOT, would produce enduring reductions in plasma corticosterone (Petersson et al., 1999) and an upregulation of plasma OT (Bowen et al., 2011; McGregor & Bowen, 2013), providing a 'boost' in the functionality of the OT system.

Methods

Subjects

The subjects were 32 experimentally naïve male Long Evans rats (*Rattus Norvegicus*) (Adelaide University, Adelaide, Australia). Upon arrival, rats were handled for six days prior to the start of experimentation (PND 28), generally accepted as the first day of adolescence in rats (Spear, 2000). The rats were maintained in a temperature- (22 ± 1 °C) and humidity-controlled colony room with a 12-hour reverse light cycle (lights on at 21:00 h). To control for litter effects, rats were randomly assigned to three treatment groups: OT (n = 10), TGOT (n = 10), and Vehicle (n = 12). Rats were housed in groups of eight per cage, counterbalanced for treatment, with food and water available *ad*

libitum except during short testing procedures. All experimental procedures were approved by the University of Sydney Animal Ethics Committee.

Drugs and administration

OT and TGOT were obtained from Auspep Ltd. (Parkville, VIC, Australia) and stored at −20°C. Both drugs were dissolved in saline (0.9%) and injected IP at a dose of either 0.5 or 1 mg/kg every third day. Rats were assessed for various acute behavioral effects of some of these doses (see Fig. 1 for overview of schedule). The 0.5–1 mg/kg OT dose was chosen on the basis of a range of studies showing effectiveness in altering behavior and producing brain activation (Bowen et al., 2011; Carson et al., 2010; Hicks et al., 2012). Additionally, 0.5 mg/kg was of interest given that this dose strongly enhanced social interaction in Long Evans rats in a recent study (Ramos et al., 2013). Since OT and TGOT have very similar affinity for the OTR (Elands et al., 1988; Lowbridge et al., 1977) and appear to have similar behavioral potency when given ICV (Sala et al., 2012), we used equivalent doses of each peptide in this study.

Acute behavioral tests

Social play

On PND 28, 31, 34 and 55, rats were assessed for social play behavior. Testing utilized four large black plastic arenas (77 × 51 × 47 cm) with a floor of absorbent bedding. The testing room was dimly lit with a red light (40 W) and the temperature was maintained at 22 ± 2 °C. Rats were individually habituated to the arenas the day prior to the test for 30 min to overcome unfamiliarity of the testing environment. On the day of testing, pairs of rats receiving the same treatment and of approximately the same body weight (≤10 g difference), but from different home cages (i.e. unfamiliar), were placed together into the arena and tested for 20 min. The test began 5 min post-injection. Novel partner combinations were created for each test, and the time of day of testing and test chamber allocated was counterbalanced across treatment conditions. To allow for some evaluation of dose–response effects, a higher (1 mg/kg) dose of OT or TGOT was administered on PND 28 followed by a lower (0.5 mg/kg) dose on PND 31, 34 and 55 (Fig. 1).

Video acquisition software (MotMen Trackmate Quad, v4.6, Motion Mensura, Cooks Hill, NSW, Australia) recorded these sessions and a rater blind to treatment conditions scored the behaviors. Social play was scored as the duration of dyadic interactions that involved pouncing, boxing, biting the nape of the neck and wrestling the partner rat into submission (for overview, see Trezza et al., 2010). Rearing was also scored and was defined as the animal standing on hind legs, including leaning against the wall of the arena in an attempt to investigate its surroundings (Lever et al., 2006). Rearing also served as a general index of any non-specific sedative effects of drug treatment.

Emergence test

On PND 40 and 46 the rats were assessed for anxiety-like behavior using the emergence test. Again to obtain something of a dose response function, distinct 1 mg/kg and 0.5 mg/kg doses were used on these two tests (Fig. 1). The test was conducted in a large white walled arena with a black wooden floor (120 × 120 × 60 cm). A black wooden hide box (40 × 24 × 17 cm) with a hinged red Perspex lid was placed against the center of one wall. Two spotlights (150 W) illuminated the arena to produce a bright open field that is aversive to rats. Each rat was individually tested for 5 min after being placed inside the hide box. Scored behaviors included time spent in: (a) the open field; (b) the hide box; (c) latency to emerge from the hide box; and (d) risk assessment (center of mass in the hide box with part or all of head in the open field).

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