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Intranasal oxytocin attenuates the cortisol response to physical stress: A dose—response study

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Summary
Introduction: Intranasal oxytocin attenuates cortisol levels during social stress inductions. However, no research to date has documented the dose—response relation between intranasal oxytocin administration and cortisol, and researchers examining intranasal oxytocin have not examined the cortisol response to physical stress. We therefore examined the effects of 24IU and 48IU of intranasal oxytocin on the cortisol response to vigorous exercise.
Method: Seventeen males participated in a randomized, placebo-controlled, double-blind, and within-subject experiment. Participants engaged in vigorous exercise for 60 min following the administration of placebo or intranasal oxytocin on three occasions. Saliva samples and mood ratings were collected at eight intervals across each session.
Results: Salivary cortisol concentrations changed over time, peaking after 60 min of exercise (quadratic: $F(1,16) = 7.349$, $p = .015$, partial $\eta^2 = .32$). The 24IU dose of oxytocin attenuated cortisol levels relative to placebo ($F(1,16) = 4.496$, $p = .05$, partial $\eta^2 = .22$) and the 48IU dose, although the latter fell just short of statistical significance ($F(1,16) = 3.054$, $p = .10$, partial $\eta^2 = .16$). There was no difference in the cortisol response to exercise in participants who were administered 48IU of intranasal oxytocin relative to placebo. Intranasal oxytocin had no effect on mood.
Conclusion: This is the first study to demonstrate that the effect of intranasal oxytocin on salivary cortisol is dose-dependent, and that intranasal oxytocin attenuates cortisol levels in response to physical stress. Future research using exogenous oxytocin will need to consider the possibility of dose—response relations.

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Oxytocin is a mammalian hormone that is produced in both magnocellular and parvocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus. Oxytocin is released in the central nervous system through terminating axonal projections within select brain areas that originate from the paraventricular and supraoptic nuclei, as well as in the periphery through the posterior pituitary gland (Gimpl and Fahrenholz, 2001). While oxytocin is traditionally known for its role in stimulating uterine contractions during parturition and milk let-down during breast feeding, there is increasing evidence that oxytocin regulates affiliative behavior in humans (Young and Zuoxin, 2004; Bartz and Hollander, 2006; Ross and Young, 2009; Campbell, 2010).

It has been hypothesized that one way oxytocin promotes affiliative behavior is through actions on the hypothalamic—pituitary—adrenal (HPA) axis. Taylor et al. (2000) contend that oxytocin facilitates approach behavior in a social context by lowering arousal levels. This hypothesis was originally put forth in the context of a review of animal research, where the effect of oxytocin on the attenuation of HPA-activity is well established. For example, adult virgin female Wister rats display increased ACTH and corticosterone levels following swim stress after being treated with central infusion of an oxytocin antagonist (Neumann et al., 2000b), and this effect has been replicated in male rats (Neumann et al., 2000a; Ebner et al., 2005). It has also been shown that exposure to swim and restraint stress upregulates the expression of oxytocin receptors in the amygdala (Liberzon and Young, 1997), and that exposure to repeated swim stress upregulates the expression of oxytocin receptors in the hippocampus (Liberzon and Young, 1997; Leuner et al., 2012). This research has led many to speculate that oxytocin may play a key role in the regulation of HPA-activity (for a comprehensive review, see Engelmann et al., 2004; DeVries et al., 2007; Neumann, 2009).

The effect of oxytocin on the HPA-axis in humans has only recently been investigated. Cortisol, a hormone that is released by the adrenal glands during strenuous physical or psychological challenge (de Kloet et al., 2005), is a reliable biomarker of the stress response in experimental research (Foley and Kirschbaum, 2010). Consistent with the hypothesis that oxytocin lowers physiological arousal in humans, intranasal administration of oxytocin—a method that is widely used on the basis of a study that shows intranasal administration of vasopressin, which is similar in structure to oxytocin, increases its concentration in the cerebrospinal fluid (Born et al., 2002)—decreases cortisol levels during interpersonal stress (Ditzen et al., 2009; Quirin et al., 2011; Linnen et al., 2012) and during the recovery phase following a public speech stressor (Heinrichs et al., 2003). Interestingly, oxytocin infused in the periphery also attenuates basal levels of cortisol in response to exercise, suggesting possible inhibitory action at the level of the adrenal gland, since oxytocin administered in the periphery does not cross the blood—brain barrier (Legros et al., 1982, 1984, 1987; Coiro et al., 1988). Thus, it appears oxytocin can attenuate HPA activity in humans, even in response to non-psychological stressors.

An important limitation of the research on intranasal oxytocin administration in humans is that few studies have examined dose—response relations. Dose-dependent effects of oxytocin on cortisol levels have been observed in animal studies. For example, centrally administered oxytocin in animals dampens the corticosterone response to white noise stress in a quadratic fashion (i.e. small doses lower cortisol, but doses much larger than 10 ng/h do not increase the magnitude of this effect; Windle et al., 1997). Similarly, administration of large doses of intranasal oxytocin (200 μg) fails to attenuate activation of the HPA-axis in primates, while there is evidence for attenuation with chronic smaller doses (50 μg; Parker et al., 2005). In humans, the administration of oxytocin in the periphery dampens cortisol in a linear fashion (i.e. cortisol concentrations in the plasma decrease as oxytocin concentration increases, up to a dose as high as 128mIU/min; Legros et al., 1984). Despite documented dose—response relations, human research studies have utilized a wide range of doses of intranasal oxytocin, from 20IU (Bruins et al., 1992) to as high as 60IU (Fehm-Wolfsdorf et al., 1988), with no apparent rationale or theoretical justification. Two recent studies have even published work on intranasal oxytocin in humans using doses as low as 16IU (Van Ijzendoorn et al., 2011; Riem et al., 2012). Importantly, dose—response relations for the effects of intranasal oxytocin in humans cannot currently be studied using meta-analysis (Van Ijzendoorn and Bakermans-Kranenburg, 2012) because there are too few studies published on intranasal oxytocin in humans, and thus there is a need for further experimental work in this area.

In the current study, we investigated whether the effect of intranasal oxytocin administration on the cortisol response to vigorous exercise is dose-dependent. We utilized a dose of 24IU because it is the most commonly reported dose in the literature, and then doubled it for our higher dose. Moreover, the 48IU dose was large enough to capture the upper range of doses most commonly reported in the literature (Macdonald and Macdonald, 2010). We investigated both doses of intranasal oxytocin relative to placebo in a double-blind, randomized, placebo-controlled, and within-subject design. We employed a physical stress paradigm in the current study for two reasons. First, there is no habituation when participants repeatedly exercise at high intensity, as occurs when participants are repeatedly exposed to psychosocial laboratory stressors (Foley and Kirschbaum, 2010). This makes the current investigation amenable to a within-subject design, which is a more robust test of dose—response effects than a between-subject design. Second, while oxytocin has previously been shown to attenuate cortisol levels during exercise when administered intravenously (Legros et al., 1987; Coiro et al., 1988), this has never been demonstrated following intranasal administration of oxytocin. We hypothesized that intranasal oxytocin would attenuate cortisol rise in response to exercise consistent with the literature reviewed above. However, since there are no published data comparing the effect of different doses of intranasal oxytocin on cortisol in healthy humans, we had no specific hypotheses concerning the direction of the dose—response effects. As an additional consideration of our hypotheses, we measured participants' mood in response to exercise to rule out the possibility that oxytocin-induced changes in cortisol were elicited by putative effects of oxytocin on mood.

1. Method

1.1. Participants

Seventeen men, aged 18—30 (mean ± SD; 23.1 ± 3.5) years, were recruited from the community through online classified