TECHNICAL COMMENTARY

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Oxytocin

Introduction

Oxytocin is a neuromodulatory neuropeptide that is important for processing emotional stimuli in a social context. It is known for its role in facilitating trust and attachment between individuals as well as its involvement in behaviours such as mother-infant bonding, theory of mind, and empathic abilities. The impact of oxytocin may be moderated by features of the social environment or individual differences.

Blood levels of oxytocin have been found to be reduced in people with PTSD and administration of intranasal oxytocin has been shown to improve aspects of social cognition including emotion recognition, interpersonal trust, and prosocial affiliative behaviour.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2010 that report results separately for people with PTSD. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. When multiple copies of reviews were found, only the most recent version was included. We prioritised reviews with pooled data for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews with less than 50% of items checked have been excluded from the library. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found one systematic review that met our inclusion criteria[3].

- Moderate to low quality evidence found intranasal oxytocin may enhance cognitive and empathic abilities but has no effect on PTSD symptoms. Intranasal oxytocin may be effective for the regulation of sympathetic nervous tone and cortisol reactivity.

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TECHNICAL COMMENTARY

Oxytocin

Giovanna G, Damiani S, Fusar-Poli L, Rocchetti M, Brondino N, de Cagna F, Mori A, Politi P

Intranasal oxytocin as a potential therapeutic strategy in post-traumatic stress disorder: A systematic review

Psychoneuroendocrinology 2020; 115: 104605

View review abstract online

Comparison	**Intranasal oxytocin vs. placebo for PTSD.**
Summary of evidence	**Moderate to low quality evidence (small samples, direct) found intranasal oxytocin may enhance cognitive and empathic abilities but has no effect on PTSD symptoms. Intranasal oxytocin may be effective for the regulation of sympathetic nervous tone and cortisol reactivity.**

All outcomes

1 study (N = 43) found a significant reduction of skin conductivity and electromyography response to personal combat imagery with oxytocin. There was no effect on heart rate response.

1 study (N = 28) found intranasal oxytocin significantly attenuated the aberrant alpha activity in dorsolateral prefrontal regions implicated in working memory and cognitive control, in trauma-exposed veterans. Aberrant alpha activity also correlated with the number of reexperiencing symptoms (flashbacks, sensory-based memories, uncontrolled reliving of trauma). There was no effect on PTSD symptoms other than re-experiencing.

1 study (N = 37) found oxytocin administration dampened left amygdala reactivity toward all emotional faces. The intranasal oxytocin group showed enhanced left thalamus activity and increased functional coupling between left thalamus and amygdala. Patients also rated all pictures as more positive during the task. There were no drug-gender interactions.

1 study (N = 40) found intranasal oxytocin increased neural responses during reward and loss anticipation in both PTSD patients and trauma-exposed controls in the striatum, insula, and right dorsal anterior cingulate cortex, key regions in the reward pathway. In PTSD patients, intranasal oxytocin increased reward responses within the right putamen and left anterior insula, which became similar to those shown by controls. Post-hoc analysis showed a drug effect on reducing anhedonia in the PTSD group. There was no effect on reaction time.

1 study (N = 32) found intranasal oxytocin enhanced compassion toward women, both those with PTSD and controls, while it did not affect compassion toward men, in both men and women participants. There were no differences between intranasal oxytocin and placebo in recognition of any emotion or Theory of Mind.

1 study (N = 35) found intranasal oxytocin significantly attenuated PTSD symptoms triggered by trauma-script exposure. Intranasal oxytocin elicited an increase in baseline heart rate, maximum heart rate, and stress-induced increase in heart rate, as well as a reduction of pre-ejection period.

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Oxytocin

There was no effect on heart rate variability. 1 study (N = 34) found PTSD patients performed worse than controls on the n-back task under placebo, while the difference was eliminated in the intranasal oxytocin condition. Intranasal oxytocin increased connectivity between DLPFC and anterior cingulate during the task. 1 study (N = 67) found the intranasal oxytocin group showed less cortisol reactivity in response to the Trier social stress test. Intranasal oxytocin did not reduce alcohol craving patients with an alcohol use disorder. 1 study (N = 17) found trauma exposure severity was correlated with the dampening effect of intranasal oxytocin on amygdala reactivity to fearful faces. 1 study (N = 17) found no effects on PTSD and depression symptoms. No adverse effects in the oxytocin group were observed. 1 study (N = 47) found no significant drug effects.	
Consistency in results‡	Not reported
Precision in results§	Not reported
Directness of results‖	Direct

Explanation of acronyms

N = number of participants

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[4].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[4].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[5]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship

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between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[4];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[6].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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