

## REVIEW

# Oxytocin and opioid antagonists: A dual approach to improving social behavior

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## Abstract

Social behavior is a cornerstone of mental health and well-being, shaped by complex neuromodulatory processes. Pharmacological interventions targeting social deficits have largely centered around oxytocin (OT). While some clinical trials have shown promising results for OT in addressing social impairments, others have reported inconsistent outcomes, with concerns about its weak and variable effects. The central OT system is exceptionally complex, given its interactions with several neuromodulatory systems. This review explores the dynamic relationship between the OT and opioid systems in regulating social behavior and their potential therapeutic applications. Despite the known physiological relationship between the opioid and OT systems, many questions about the effects of their interaction on social behavior remain unanswered. Recent research investigating the combined effects of OT and opioid antagonists has reported promising results in improving social functioning. Here, we highlight key challenges in this area, including how to manipulate the OT and opioid systems without disrupting their natural balance, understanding their role in real-world social contexts, and achieving precise modulation of their effects. Evaluating these points will require cutting-edge neuroscience techniques, such as optogenetics, CRISPR, and designer ligands, to refine our understanding and pave the way for novel therapeutic strategies to improve social functioning.

## KEYWORDS

autism spectrum disorder, combinatorial neuropharmacology, naloxone, opioid antagonist, opioid system, oxytocin system

## INTRODUCTION

Social behavior is crucial for shaping our well-being and mental health, and a deep understanding of the neural substrates underlying social behavior is necessary for developing effective therapeutic approaches.<sup>1</sup> Neuromodulators and hormones are well-known regulators of social behavior, with the neuropeptide oxytocin (OT), synthesized by du Vigneaud in 1954,<sup>2</sup> recognized as one of the

most significant neuromodulators influencing social behaviors.<sup>3</sup> OT, commonly known as “the social hormone,” has intrigued researchers for over a century,<sup>4</sup> initially for its role in facilitating childbirth and lactation in mammals and later for its involvement in maternal care and pair bonding.<sup>5,6</sup> Moreover, a study in 2005 showed that intranasal OT administration in male participants increased trust behaviors,<sup>7</sup> suggesting a role for OT in high-level social cognition. However, more investigations are needed as later studies analyzing a larger dataset failed to replicate these initial results.<sup>8,9</sup> Around that time, numerous human studies had investigated the effects of OT on emotion

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recognition, theory of mind, social memory, and several other social behaviors, suggesting that OT enhances social abilities and facilitates positive social interactions.<sup>10</sup> Indeed, the impact of OT in social neuroscience has grown remarkably, with the number of related publications increasing from just 10 in 2005 to over 200 by 2019, a trend that has remained consistent in recent years.<sup>11</sup>

The OT system in the brain is exceptionally complex<sup>12–14</sup> and its interactions with other neuromodulatory systems are critical yet not fully understood. For instance, the OT system interacts with the serotonin system.<sup>15–17</sup> Evidence suggests bidirectional influences between OT and serotonin: increasing central serotonin levels raises peripheral OT concentrations,<sup>18–20</sup> while OT application in the raphe nucleus enhances serotonin release.<sup>21</sup> Anatomical overlap between serotonin transporter fibers and OT-releasing cells in the hypothalamus further supports their functional interdependence.<sup>22</sup> Impairments in the relationship between serotonergic and OT systems seem to be linked to the development of social dysfunction in autism spectrum disorder (ASD). For example, hyperserotonergic and hypooxytocinergic biomarkers have been linked to ASD.<sup>23</sup> In humans, intranasal OT modulates 5-HT<sub>1A</sub> receptor binding in regions involved in social motivation, such as the amygdala and orbitofrontal cortex,<sup>24</sup> but this effect is absent in individuals with ASD despite similar receptor concentrations.<sup>25</sup> In rodent ASD models, enhancing serotonin improves social behaviors, but these effects can be blocked by OT antagonists, underscoring the importance of OT–serotonin coordination.<sup>26</sup>

Furthermore, the interplay between OT and the dopamine system is critical in regulating prosocial behaviors, reward processing, and social bonding.<sup>27,28</sup> OT modulates dopaminergic activity in key reward-related regions, including the ventral tegmental area (VTA), nucleus accumbens (NAcc), ventral pallidum, and dorsal and ventral striatum. These interactions are crucial for reinforcing prosocial behaviors and social bonding. In rodent models, OT release during social contact enhances dopamine signaling in the NAcc, amplifying the salience of social stimuli and affiliative behaviors such as pair bonding and maternal care.<sup>29,30</sup> The VTA, a primary source of dopamine, receives modulatory input from oxytocinergic projections, which can potentiate dopaminergic reward responses during social interactions.<sup>31,32</sup> Additionally, this interplay is implicated in social memory formation, as OT enhances dopaminergic activity to facilitate the recognition and preference for familiar conspecifics.<sup>33,34</sup> Disruptions in the OT–dopamine pathway have been linked to impairments in social behavior, such as those observed in ASD and social anxiety, underscoring its importance in the neural circuitry of regulating social behavior.<sup>35,36</sup>

In addition to its interactions with serotonin and dopamine, OT also plays a significant role in modulating the activity of sex hormones such as estrogen, progesterone, and testosterone.<sup>37</sup> It influences these hormones by regulating their receptor concentrations and signaling dynamics, creating a complex interplay that affects various physiological and behavioral processes.<sup>38</sup> For instance, estrogen has been shown to upregulate OT receptor expression, potentially amplifying OT's effects.<sup>39</sup> Moreover, estrogens regulate social learning and interact with OT in mediating social recognition.<sup>40</sup> Interestingly, OT can

also influence testosterone levels—intranasal OT administration has been shown to increase blood plasma testosterone levels in healthy men.<sup>41</sup> Furthermore, in men (but not in women), testosterone levels are strongly linked to competitiveness. However, this association disappears following OT administration, suggesting a modulatory role of OT in testosterone-driven competitive behavior.<sup>42</sup> These hormonal interactions contribute to variability in social, emotional, and cognitive responses to OT and can potentially explain some of the sex differences observed upon OT administration, which we explore in more detail later in this review.

Given its influence on the reward-related pathways, it is not surprising that OT interacts with the opioid system in regulating social behavior.<sup>43</sup> Opioids directly inhibit OT secretion in mammals by acting in the hypothalamus and posterior pituitary.<sup>44,45</sup> During parturition, endogenous opioids tightly control OT release into both the blood and brain,<sup>46</sup> with morphine delaying parturition and reducing circulating OT levels.<sup>47–49</sup> In contrast, naloxone (NAL), a  $\mu$ -opioid receptor antagonist, reverses these effects by accelerating parturition and significantly increasing OT release.<sup>47,49</sup> However, the interaction between the OT and opioid systems extends beyond reproductive behaviors. Some studies suggest that OT's effects on social bonding may partially depend on the opioid system.<sup>50,51</sup> Other research proposes that OT enhances social behavior by increasing  $\mu$ -opioid signaling<sup>52</sup> and promoting social rewards.<sup>53</sup> This makes the interaction between OT and NAL a key area of interest for understanding the neurochemical basis of social behavior. Finally, Dal Monte et al. provided compelling evidence of the functional link between OT and the opioid system and its effect on social attention.<sup>54</sup> They reported that the combined administration of OT and NAL led to a supralinear enhancement of selective social attention in rhesus monkeys, yielding effects greater than the sum of each compound administered separately. These findings suggest that the co-administration of exogenous OT and NAL may improve social functions by leveraging endogenous OT release.

In this review, we will focus on the individual and combined effects of OT and NAL on social behavior. By examining the regulatory relationships between the oxytocinergic and opioid systems in the brain, we aim to provide a framework for understanding the neurobiological mechanisms underlying social interactions and identify potential therapeutic avenues to address social deficits. To uncover how OT and NAL work together to regulate social behavior and translate this knowledge into effective therapies, several key challenges must be addressed: (1) determining how to manipulate the tightly regulated oxytocinergic and opioid systems exogenously without disrupting their endogenous homeostatic balance; (2) understanding how these systems function within the complex, context-dependent dynamics of real-world social interactions; and (3) achieving precise temporal control over their modulation to elicit targeted and precise effects. Addressing these challenges will require leveraging cutting-edge neuroscience technologies, including optogenetics, CRISPR, and designer ligands. These tools offer great potential to refine our understanding and manipulation of these systems and promote the development of innovative interventions to enhance social functioning.

## OT AND NAL: FROM INTRACELLULAR INTERACTIONS TO BEHAVIOR

OT, a neuropeptide consisting of only nine amino acids and synthesized in the paraventricular and supraoptic nuclei of the hypothalamus,<sup>55,56</sup> plays a pivotal role in both peripheral and central functions.<sup>57,58</sup> Peripherally, it is released into the bloodstream, regulating physiological processes ranging from maternal behavior, such as uterine contractions during parturition and milk ejection during lactation,<sup>59,60</sup> to more general physiology and perception, like nociception, analgesia, and general energy balance.<sup>61–63</sup> Centrally, OT acts as a neurotransmitter and neuromodulator, influencing a wide range of social, emotional, and cognitive processes.<sup>12,64</sup> The magnocellular neurons that synthesize OT project to critical brain regions involved in social behavior and reward processing, including the amygdala, striatum, ventral pallidum, and prefrontal cortex.<sup>29,65–67</sup> These projections support OT's role in modulating social bonding, fear and stress responses, and social decision-making.<sup>33,68,69</sup>

The evolutionary significance of OT is emphasized by the fact that it plays a critical role in modulating social behavior across a wide range of species.<sup>70,71</sup> In rodents, the OT system mediates the formation of pair-bonding in monogamous prairie voles,<sup>72–76</sup> promotes maternal and social behaviors,<sup>13,77,78</sup> and is crucial for the ability to recognize conspecifics.<sup>79</sup> Additionally, OT has been shown to induce atypical behaviors, such as nest building in virgin female rats,<sup>80</sup> while the use of an OT antagonist can delay the onset of maternal behavior after pup delivery.<sup>81</sup> Finally, OT receptor knockout mice, compared to the wild type, emit fewer ultrasonic vocalizations in response to social isolation, experience deficits in social discrimination ability, and display more aggressive behavior.<sup>82</sup>

Several studies in bonobos and chimpanzees have reported a link between urinary OT levels and key social behavior such as cohesion, grooming, and sexual behavior.<sup>83–88</sup> More recently, the administration of OT to bonobos via a nebulizer has been shown to influence positive behaviors during naturalistic interactions, enhancing social gaze, eye contact,<sup>89</sup> and grooming.<sup>90</sup> In nonhuman primates, OT can impact a wide range of social behaviors.<sup>91</sup> In macaques, OT enhances social attention by increasing the time spent looking at conspecifics' eyes,<sup>92,93</sup> promoting gaze-following behaviors,<sup>94</sup> and reducing attention to negative facial expressions<sup>95</sup> and social threats.<sup>96</sup> Moreover, OT can improve socially reinforced learning,<sup>97</sup> modulate prosocial preferences,<sup>98,99</sup> and affect social hierarchy.<sup>100</sup>

In humans, OT has been reported to enhance eye- and face-directed gaze,<sup>101</sup> improve the ability to infer mental states,<sup>102,103</sup> and facilitate socially reinforced learning.<sup>104</sup> Moreover, OT increases trust and cooperative behaviors in social interactions<sup>7,105</sup> and improves social memory, enabling individuals to recognize familiar faces and process social cues.<sup>32,106,107</sup> Additionally, OT attenuates amygdala activity in response to aversive stimuli,<sup>102,108–110</sup> highlighting its role in regulating emotional responses within social contexts.

Taken together, these findings have stimulated interest in the potential therapeutic applications of exogenous OT, positioning it as a promising pharmacological agent for psychiatric disorders char-

acterized by social dysregulation. Disorders such as borderline personality disorder,<sup>111,112</sup> post-traumatic stress disorder,<sup>113</sup> and schizophrenia<sup>114</sup> have been highlighted as potential targets for OT-based treatments. Additionally, OT has shown promise in addressing core symptoms of ASD, including reducing repetitive behaviors, enhancing appropriate social interactions, improving affective speech comprehension, and partially mitigating deficits in theory-of-mind abilities.<sup>102,115–118</sup> While some clinical trials have produced encouraging results regarding OT's efficacy in ASD treatment,<sup>119–121</sup> others have reported less conclusive findings.<sup>122,123</sup>

Despite its potential, the therapeutic benefit of OT remains uncertain due to inconsistent evidence, methodological limitations, and replication challenges.<sup>124</sup> Concerns include whether intranasal OT effectively crosses the blood–brain barrier (BBB) and the extent to which it reaches the central nervous system, as well as the lack of quantified dose–response data for OT's effects on specific social behaviors.<sup>125</sup> Additionally, some studies lack methodological rigor, with inadequate statistical power for detecting a wide range of effect sizes, insufficient replication, and the absence of preregistered protocols.<sup>126–129</sup> These concerns call for the need to develop standardized and validated OT assays to enhance cross-study comparability<sup>130</sup> and precise investigations into dose–response relationships to disentangle the pharmacological and physiological effects of intranasal OT administration.<sup>131</sup> Consequently, research on intranasal OT is undergoing a critical reassessment to refine methodologies and clarify its clinical potential.<sup>125,130,131</sup>

## Opioids and social behavior

The opioid system has also been critically implicated in regulating social behavior. Opioid receptors are classified into three primary subtypes— $\mu$ -,  $\delta$ -, and  $\kappa$ -receptors—which are widely distributed across reward-related brain regions.<sup>132,133</sup> The opioid system, particularly the  $\mu$ -opioid receptors that are strongly expressed in limbic regions in the primate brain,<sup>133,134</sup> are linked to social reward, social affiliation, and social bonding.<sup>135–139</sup>

One of the earlier studies investigating the involvement of the opioid system in social behavior examined the distress exhibited by both adult and infant guinea pigs following maternal separation. This study found that subcutaneous morphine injections, a  $\mu$ -opioid receptor agonist, reduced the distress displayed, while NAL intensified it.<sup>135</sup> Also, juvenile rats display an increased amount of social play and interaction post-isolation, an effect that is further enhanced by low-dose morphine administration.<sup>140,141</sup> In contrast, NAL administration has been shown to reduce social play and fighting behavior in rats raised in isolation.<sup>142,143</sup> Blocking  $\mu$ -opioid receptors pharmacologically has been shown to disrupt social bonding in rodents, impairing behaviors such as partner preference formation and maternal retrieval of pups.<sup>144,145</sup> Additionally, activation of  $\mu$ -opioid in the nucleus accumbens and ventral pallidum—reward-related regions—mediates the hedonic and reinforcing properties of social interactions and affiliative behaviors.<sup>139,146</sup> A study in mice found that pups with a

homozygous  $\mu$ -opioid receptor knockout (*Oprm1*<sup>-/-</sup>) show a deficiency in recognizing maternal cues and ultrasonic vocalizations associated with maternal bonding.<sup>147</sup> Similarly, both male and female *Oprm1*<sup>-/-</sup> and *Oprm1*<sup>+/-</sup> mice showed reduced social interactions and altered social preferences compared to wild-type mice.<sup>148</sup>

The tight link between the opioid system and social behavior has been investigated in nonhuman primates as well. In monogamous titi monkeys, morphine was shown to decrease the initiation of social contact by males toward females.<sup>149</sup> In talapoin monkeys, social grooming was shown to increase beta-endorphin (an endogenous opioid) levels in cerebrospinal fluid (CSF)<sup>150</sup>. In macaques, pharmacological studies further elucidate this link: administration of morphine reduces both grooming solicitations and the amount of grooming received. In contrast, NAL enhances social behaviors by increasing grooming solicitations,<sup>151,152</sup> promoting proximity between juveniles and their mothers,<sup>153</sup> and elevating clinging behaviors in infants after maternal separation (by naltrexone, a less-selective  $\mu$ -opioid receptor antagonist)<sup>154</sup>. Moreover, a study in wild rhesus macaque colonies found that infants with the gain-of-function polymorphism C77G in the *OPRM1* gene exhibited increased distress during maternal separation and spent more time with their mothers upon reunion, compared to infants homozygous for the C allele.<sup>155</sup> Mothers with the G allele also exhibited more frequent restraint of their infants and showed higher OT levels in their CSF during lactation, relative to those homozygous for the C allele.<sup>156</sup>

The role of  $\mu$ -opioid receptors in humans can be investigated using receptor-specific radioligands in combination with positron emission tomography (PET).<sup>157</sup> For instance, a study investigating healthy male and female human adults showed that attachment avoidance was negatively correlated with  $\mu$ -opioid receptor availability in key brain regions, including the thalamus, anterior cingulate cortex, frontal cortex, amygdala, and insula.<sup>158</sup> Another study found that receiving an affective touch from a partner decreased endogenous  $\mu$ -opioid receptor binding in these same regions, making those receptors available for PET ligand binding.<sup>159,160</sup> Social rejection can also trigger the  $\mu$ -opioid system by increasing receptor activity in the ventral striatum, amygdala, midline thalamus, and periaqueductal gray (PAG).<sup>136</sup> Moreover, the  $\mu$ -opioid system can also inhibit the acquisition of a new threat based both on fear-conditioning as well as observational fear learning.<sup>161,162</sup> Genetic studies on the A118G functional polymorphism of the *OPRM1* gene have revealed that individuals carrying the G allele exhibit heightened sensitivity to social rejection<sup>163</sup> and a greater propensity for engaging in affectionate relationships.<sup>162,164</sup> Though these results show a clear indication of the opioid system being associated with social behavior, specific results should be carefully interpreted since these genes are multifunctional and their roles and prevalence vary highly across populations and experimental conditions.

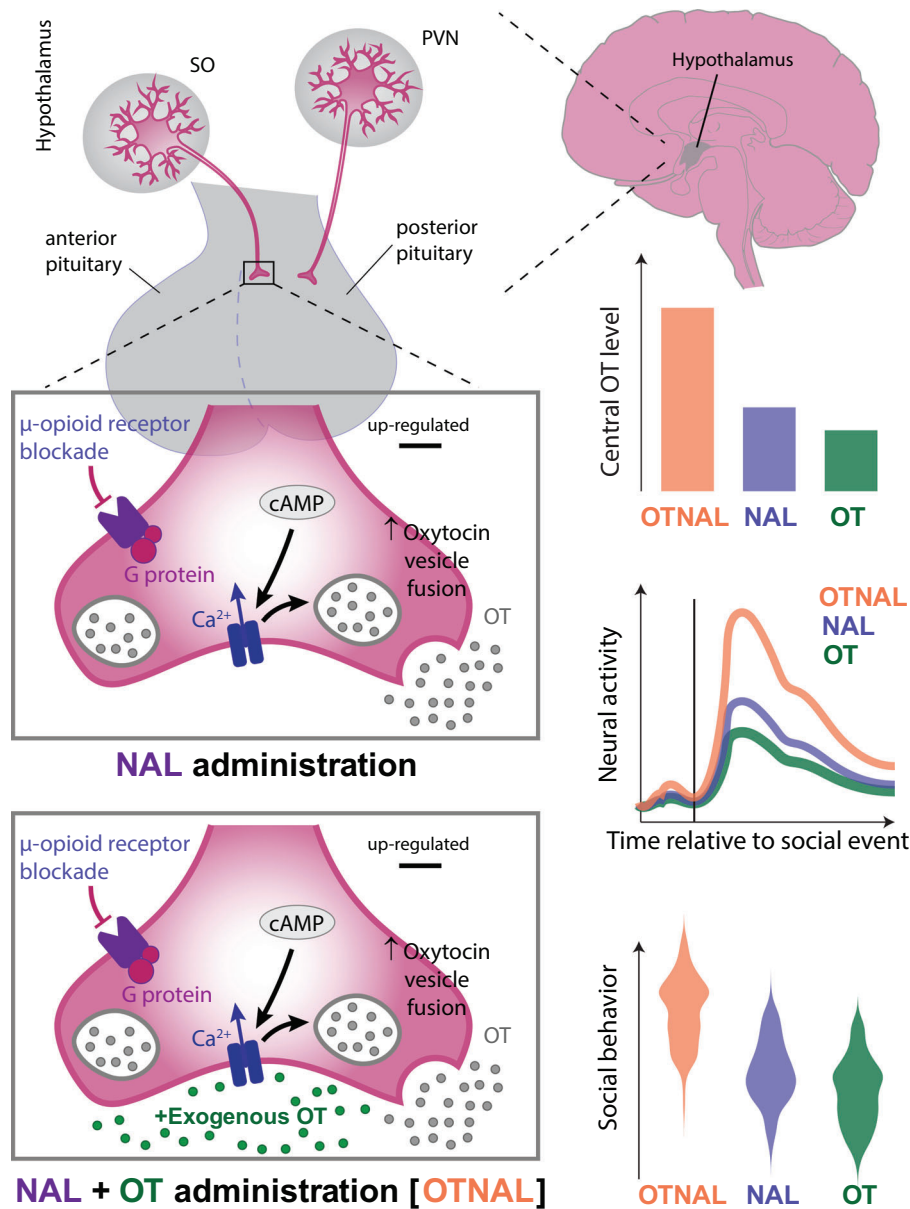
Opioid antagonists in humans have been proposed in the past to potentially treat social deficits in ASD. Many (but not all) individuals with ASD display a dysfunction in the pineal-hypothalamic-pituitary-adrenal axis, and such dysfunction involves hypersecretion of brain opioids, including endorphins.<sup>165</sup> Naltrexone, though less selective

to the  $\mu$ -opioid receptor than NAL, has been used successfully to decrease self-injurious behavior, stereotypies, hyperactivity, and withdrawal while increasing verbal production and attentiveness.<sup>166,167</sup> In general, opioid blockers have yielded promising but preliminary results in promoting social behavior by increasing social communication, proximity-seeking, and social interactions.<sup>168,169</sup> However, other studies have reported that opioid antagonist administration can reduce social bonding, diminish pleasure derived from social interactions, and even increase feelings of social isolation.<sup>170,171</sup> The inconsistencies in the direction in which social behavior is altered upon administration of NAL in humans and nonhuman animals can potentially be explained by the fact that opioid receptors signaling can display disparate downstream effects depending upon whether an individual is under stress. Since the opioid signaling system is involved in both the neural circuits governing analgesia<sup>172</sup> and those related to reward processing,<sup>173</sup> an individual's social behavior may vary depending on their stress levels. Heightened social behavior may be driven by the pain-relieving effects of opioids, while reduced social reward-seeking could result from opioid-saturated reward signaling. Indeed, a state-dependent hypothesis has recently been put forward with the goal of explaining this seemingly complex directional effect of the  $\mu$ -opioid system on social behavior. According to this model, how the  $\mu$ -opioid system modulates social motivation critically depends on one's behavioral state (e.g., distressed or comforted), leading to diverse directional effects on social behavior.<sup>174</sup>

In conclusion, although the  $\mu$ -opioid system is recognized as a crucial player in social behaviors, the existing body of research is still relatively sparse and inconsistent. Furthermore, numerous studies have presented a convoluted understanding of how both opioid antagonists and agonists specifically influence social behavior. The effects of the opioid system appear to be significantly influenced by factors such as the state of the individual,<sup>174</sup> the context in which interactions occur,<sup>175,176</sup> and the dosage administered.<sup>177</sup> These elements seem to play a pivotal role in determining how opioid receptors modulate social behaviors.<sup>178</sup> Crucially, given that much of the knowledge stems from animal models,<sup>179,180</sup> it is imperative that future research bridge the gap between nonhuman animal and human studies.<sup>51</sup> This will not only enhance our understanding of the  $\mu$ -opioid system's function in social contexts but also facilitate the development of effective interventions for social dysfunctions associated with opioid dysregulation.

## Combination of OT and NAL in social behavior

One mechanism by which the opioid system affects social behavior is via its regulatory coupling with OT (Figure 1). Indeed, the physiological relationship between the opioid and OT systems has been firmly established.<sup>181</sup> Animal studies have revealed that opioids directly inhibit OT secretion in mammals by acting on the posterior pituitary and the hypothalamus.<sup>44,45</sup> In rodents, opioids suppress OT release from axon terminals in the posterior pituitary and reduce the activity of OT neurons via their actions on neuronal cell bodies in the hypothalamus.<sup>182,183</sup> Chronic administration of morphine, a classic



**FIGURE 1** Combinatorial effect of oxytocin (OT) and  $\mu$ -opioid antagonist at the functional and behavioral level. On the left are illustrations of the cellular and synaptic mechanisms mediating the regulation of endogenous OT secretion by  $\mu$ -opioid receptors (only G protein signaling at the presynaptic site is shown). SO represents supraoptic nucleus, and PVN represents paraventricular nucleus. On the right are hypothesized consequences arising from the administration of intranasal naloxone (NAL) with intranasal OT (OTNAL), NAL alone, or OT alone on central OT levels, the neural activity of downstream brain regions, and social behavioral effects expected based on Refs. 54 and 178. Figure adapted from Refs. 198–200.

$\mu$ -opioid receptor agonist, also affects OT synthesis and secretion.<sup>184</sup> During parturition, endogenous opioids tightly regulate OT release into both the bloodstream and brain.<sup>46</sup> Morphine delays parturition by reducing circulating OT levels, while opioid activity attenuation with NAL accelerates parturition and increases OT release.<sup>48,49</sup> Opioids also disrupt milk ejection during lactation in rodents by inhibiting OT secretion in neural tissues.<sup>185,186</sup> Although OT and vasopressin are synthesized in the same magnocellular neurons of the hypothalamus,<sup>46</sup> opioids selectively regulate OT release. For instance, endogenous opioid inhibition triggers central OT but not vasopressin release,<sup>46</sup> and

the high-affinity  $\mu$ -opioid receptor antagonist NAL strongly stimulates OT release from the posterior pituitary without affecting vasopressin release.<sup>44</sup> Moreover, morphine withdrawal induces rapid OT gene transcription in magnocellular supraoptic neurons. This transcriptional upregulation is preceded by increased c-fos gene activity and its elevated protein expression in OT neurons within the supraoptic nucleus.<sup>187</sup> Collectively, these findings provide strong evidence for the cellular-level modulation of the OT system by the opioid system.

The OT and opioid systems interact closely in the brain to regulate several aspects of social behavior, such as bonding, affiliative interac-

tions, and emotional responses.<sup>188</sup> In the NAcc and ventral pallidum, OT signaling amplifies the release and efficacy of endogenous opioids in rodents, reinforcing positive social interactions such as pair bonding and caregiving.<sup>146,189</sup> Blocking  $\mu$ -opioid receptors has been shown to reduce OT's ability to promote affiliative behaviors, such as partner preference formation and maternal care.<sup>145</sup> The interplay between OT and  $\mu$ -opioid receptors also modulates emotional responses to social stress and rejection. Social rejection and social pain in humans are associated with decreased  $\mu$ -opioid receptor availability in several brain regions, including the ventral striatum, amygdala, midline thalamus, and PAG.<sup>136,190</sup> A recent study conducted by Harder and colleagues has highlighted the complex relationship between prenatal opioid exposure, social behavior, and OT expression.<sup>53</sup> Prenatal morphine exposure in rodents significantly altered social behaviors, such as social attachment, play activities, and aggressive interactions, and resulted in lower OT expression in early postnatal days compared to controls.<sup>53</sup> The initial decrease in OT levels may contribute to the observed deficits in social attachment and play behaviors, while the later increase in OT expression could suggest a compensatory mechanism or altered neurodevelopmental trajectory in response to early morphine exposure. These findings provide compelling evidence that prenatal morphine exposure negatively impacts social behaviors and alters OT expression levels in rodents, underscoring the importance of further research in this area to elucidate the underlying mechanisms and potential long-term consequences. Additionally, OT injections significantly improved social behavior in mice lacking  $\mu$ -opioid receptors, compared to wild types, particularly in social contexts.<sup>191</sup> This context-dependent effect highlights the importance of environmental factors in modulating the effects of OT on social interactions, suggesting that the presence of social stimuli may enhance the efficacy of OT treatment. Nisbett and colleagues recently found that OT administration reduced the measure of anxiety and depression-like behavior.<sup>192</sup> They also showed that blocking  $\mu$ -opioid receptors enhanced the anxiolytic-like effects of OT, while blocking  $\kappa$ -opioid receptors diminished these effects in mice. This indicates that the  $\mu$ - and  $\kappa$ -opioid receptor systems have distinct roles in modulating OT's influence on anxiety-like behaviors. Notably, NAL enhanced OT's impact on anxiety-like behavior but not on depression-like behavior. Overall, this study underscores the significance of the interaction between the opioid system and OT in emotion regulation while also highlighting distinct neural mechanisms underlying anxiety and depression.<sup>192</sup>

Though there are not many studies that investigate the combinatorial effect of opioid antagonists and OT in human and nonhuman primates, a study using an innovative gaze interaction paradigm in rhesus macaques<sup>93</sup> has investigated the interaction between the OT and opioid systems in enhancing social attention dynamics.<sup>54</sup> The combination of intranasal OT and NAL produced a supralinear effect, increasing attention to conspecific faces and eyes, particularly during dynamic social exchanges such as mutual eye contact. The supralinear effect was determined by the fact that the combination of exogenous OT and NAL enhanced interactive social attention more than the sum of each drug's effect alone. Although the authors utilized a naturalistic approach, the data were still collected in a laboratory setting. In this

context, NAL may reduce the anxiolytic effects commonly observed in animals under controlled conditions. By alleviating anxiety-related behaviors, NAL could enhance OT's role in promoting social attention, leading to greater engagement with social cues. Future studies should examine the combined effects of intranasal OT and NAL in more ecologically valid, real-world settings. Given that the neurobiological mechanisms underlying social behavior are context-dependent, it is possible that NAL could exert an opposite effect in more naturalistic environments, where social interactions unfold with greater complexity and less external restriction.<sup>174</sup>

Supporting these findings, the primary OT-releasing regions in the human brain were shown to have enriched expression of  $\mu$ -opioid receptors, suggesting a potential interaction between the two systems also in humans.<sup>54</sup> To date, the only study in humans combining exogenous OT with an opioid antagonist, naltrexone, examined the effect of this compound in treating hypothalamic obesity in a pediatric patient.<sup>193</sup> The combination therapy effectively reduced the patient's weight and improved metabolic parameters. The administration of OT was associated with decreased appetite and increased satiety, while naltrexone contributed to the reduction of food cravings.<sup>193</sup> Collectively, these studies support the hypothesis that antagonizing  $\mu$ -opioid receptors may amplify OT's effects across various biological measures.

Multiple mechanisms can be hypothesized to explain the  $\mu$ -opioid and OT interaction. First, NAL may increase the release of endogenous OT and the activity of OT neurons in the hypothalamus, as shown in the first seminal study *in vitro*.<sup>44</sup> A second hypothesis has been proposed by Putnam and Chang suggesting that OT and opioid receptors modulate social behaviors through distinct neural mechanisms, and their simultaneous activation may influence behavior at multiple levels.<sup>178</sup> For example, opioid antagonism could amplify social reward seeking potentially through dampening the neural reward circuitry, but activation instead could diminish social reward seeking in favor of drug-induced reward. As a result, opioid antagonists increase social behaviors such as grooming, possibly by enhancing social reward-seeking due to the suppression of natural reward pathways.<sup>151,152</sup> OT also influences social behaviors, typically enhancing attention to social stimuli and promoting prosocial choices.<sup>54,92,94,97,99</sup> This may be mediated by OT enhancing the saliency of social stimuli in the brain,<sup>194,195</sup> leading to neural representations of social stimuli exhibiting a higher signal-to-noise ratio and facilitating prioritized transmission across brain regions. Thus, in addition to stimulating the release of endogenous OT, NAL might increase social reward-seeking. NAL enhances social reward-seeking by blocking opioid receptors, while OT increases social stimulus saliency, leading to synergistic effects that surpass the effect of either drug alone.<sup>54,178</sup> One last hypothesis suggests a regulatory mechanism involving amygdala neurons.<sup>192</sup> This hypothesis proposes that  $\mu$ -opioid receptors may enhance the responsiveness of OT receptor-expressing neurons in the amygdala, while  $\kappa$ -opioid receptors may have the opposite effect. Previous research has demonstrated that OT,  $\mu$ -opioid, and  $\kappa$ -opioid receptors are expressed on GABAergic neurons within the amygdala.<sup>196,197</sup> Accordingly,  $\mu$ -opioid receptor antagonists, such as NAL, may disinhibit GABAergic neurons, thereby increasing OT responsiveness in the amygdala. In contrast,

$\kappa$ -opioid receptor antagonists may suppress GABAergic activity, leading to reduced OT responsiveness in this region. This regulatory mechanism mirrors similar processes observed in the hypothalamus, suggesting a comparable role for regulatory control in the amygdala. Gaining deeper insights into the combined effects of OT and NAL on social behaviors could offer new, innovative, and effective clinical approaches for enhancing social functions.<sup>198–200</sup>

## OT-NAL FOR THERAPEUTIC USAGE

The intricate interplay between OT and opioid signaling in the brain holds significant promise for developing therapies to treat neuropsychiatric disorders, particularly those characterized by social deficits, such as ASD. However, unlocking the full potential of the oxytocinergic system as a therapeutic tool requires a deeper understanding of its interactions with the opioidergic system at molecular, cellular, and circuit levels. Two critical challenges stand at the forefront of this effort. First, the field must establish methods to exogenously modulate the tightly regulated oxytocinergic and opioidergic systems without disrupting other targets in the brain, preferably with precise temporal control over these modulations to elicit desired behavioral outcomes. Second, we must gain an understanding of how these systems operate in real-world, dynamic contexts where contextual factors play a key role in determining the result of psychopharmacological manipulations.

### The challenge of designing exogenous interventions

To successfully harness the innate neurobiological substrates of the OT and opioid systems in the brain, the therapeutic application of combined OT and NAL to enhance social behavior must consider the spatiotemporal dynamics of endogenous OT release and regulation.<sup>201</sup> The dynamics of OT release within the brain are highly complex and remain understudied, particularly in specific regions and neural populations. While intracerebral microdialysis has been a valuable tool for measuring OT release in conscious, freely behaving animals,<sup>202</sup> most studies have focused on larger magnocellular neurons due to current sensitivity limitations.<sup>201</sup> This approach has revealed region-specific OT dynamics in areas like the septum, hippocampus, amygdala, and nucleus accumbens, yet accurately capturing the release patterns from smaller parvocellular neurons remains a significant challenge.<sup>203–205</sup>

Exogenous OT induces complex and time-varying effects on brain activity, with its pharmacological impact evolving dynamically following administration. Brain electrophysiology studies reveal that the effects of OT are not static; instead, they manifest at different times across post-administration windows, influencing distinct neural patterns over nearly 2 hours. For example, OT alters microstate dynamics—brief, quasi-stable neural activity patterns—starting as early as 15 min post-administration, with effects continuing at varying intensity and specificity over time.<sup>206</sup> This highlights the temporally nuanced nature of OT's neural effects and underscores the importance

of precise timing in therapeutic applications. Additionally, some studies have reported effects of OT administration lasting weeks<sup>207</sup> or even years after exposure,<sup>208</sup> further emphasizing the complexity of making temporally precise OT interventions.

The temporal pharmacodynamics of peripherally administered OT or NAL are further convoluted because exogenously administered OT faces challenges in crossing the BBB. Even to date, it remains unclear how peripheral OT administration, such as the commonly used intranasal nebulization of OT in a saline vehicle, impacts central OT levels in the brain. OT is approximately 1 kDa and hydrophilic, which limits its passive diffusion across the lipid-rich BBB. Studies in non-human primates have demonstrated that nebulized administration of OT increases CSF OT concentrations,<sup>98,99</sup> with nasal spray producing greater plasma increases than a nebulizer, though both methods elevate CSF OT similarly.<sup>209</sup> Subsequent studies have demonstrated that intranasal OT can bypass the BBB, delivering OT to specific brain regions like the striatum, which influence motivated behaviors. Using mass spectrometry, labeled OT was detected in brain areas along olfactory and trigeminal nerve pathways, while endogenous OT was found in regions associated with oxytocinergic projections.<sup>5</sup> OT may be actively transported into the brain through a process of binding to receptors for advanced glycation end products (RAGE), as studies in mice lacking RAGE in brain vascular endothelial cells show impaired OT brain uptake.<sup>210</sup> However, the effect of peripherally circulating OT on brain activity cannot be ruled out either. A study using vasoconstrictor pretreatment to block peripheral absorption revealed that intranasal OT effects on neural activity (delta-beta cross-frequency coupling) depend on peripheral vasculature-mediated routes,<sup>211</sup> suggesting that peripheral OT could indirectly influence brain function by signaling through peripheral receptors that activate pathways leading to central changes in neuromodulation. Cumulatively, these findings demonstrate that any therapeutic application of OT and NAL must precisely account for where it is binding—and over what time course—to fine-tune the neural and behavioral effects.

Similarly, endogenous OT levels within the brain are carefully regulated by release and regulation mechanisms that vary based on brain region related to extracellular or synaptic space. Evidence suggests that OT concentrations remain effective only within a limited radius of 55–120  $\mu$ M around the release site, largely ruling out long-range diffusion to distant brain regions.<sup>212</sup> The challenge of developing a combined OT and NAL therapy is further complicated by the dynamics of endogenous OT release—the putative function of NAL—which occurs through both synaptic and nonsynaptic mechanisms, including axonal, dendritic, and somatic pathways. While parvocellular neurons likely form synaptic connections, the release from magnocellular neurons appears to be primarily nonsynaptic, with OT diffusing into the extracellular space to act as a neuromodulator. This likely variation between regions could mean that therapeutic OT administration might require precise dosing or timed delivery methods to avoid disrupting these finely tuned regulatory systems. Thus, recognizing and potentially leveraging these mechanisms regionally may be essential for maximizing OT's prosocial effects without interfering with other endogenous functions.

Furthermore, the assumption that OT is evenly distributed within a solution may not hold, especially when considering its dynamics in different environments, such as the brain. A study investigating OT infusion bags used in labor revealed that, over an 8-h period, OT distribution in saline solutions was not uniform.<sup>213</sup> Samples taken from different parts of the bags showed random and unequal concentrations, with no consistent gradient or pattern. While this study focused on infusion bags, it raises critical questions about the spatial distribution of OT in more complex systems like the brain, where localized concentrations could significantly impact function. These findings highlight the need for careful consideration of the spatial dynamics of OT in therapeutic and physiological contexts.

There is a pressing need to improve the consistency and accuracy of methods used to measure neuroactive hormones like OT across studies.<sup>130</sup> Current reports of baseline hormone levels in human plasma often show extreme variability, differing by factors of 100–10,000 across publications.<sup>214</sup> This inconsistency arises partly from insufficiently detailed methodological descriptions and unclear quality control practices. Given that baseline concentrations of bioactive OT and related hormones typically range from 1 to 10 pmol/L, assays need to detect concentrations below 1 pmol/L with high precision. Measurements reporting significantly higher levels—particularly above 100 pmol/L—should be reevaluated, as such values rarely reflect physiological conditions.

It is also important to note that different assays vary in their efficacy and specificity for binding to OT, and OT itself exists in different bound states during physiological functioning. Additionally, the low half-life of OT causes its concentrations to fluctuate significantly.<sup>215</sup> Therefore, standardizing measurement techniques is essential for accurately determining hormone concentrations necessary for therapeutic applications and for establishing reliable dose–response relationships in clinical settings.

In summary, the complex spatiotemporal dynamics of endogenous OT release and regulation present a significant hurdle toward the therapeutic employment of combined OT and NAL treatments. Intranasal administration of OT presents additional complexities as it bypasses the BBB to target specific brain regions while also potentially influencing brain function through peripheral pathways. Furthermore, OT's careful regulation via homeostatic mechanisms and its uneven spatial distribution within the brain systems underscore the need for precise dosing and delivery methods. Standardizing hormone measurement techniques is essential to resolve inconsistencies in reported baseline levels and to ensure reliable, reproducible therapeutic applications.

## Context matters

Current research underscores the importance of integrating social environments into any therapeutic application of combinatorial OT and NAL.<sup>216</sup> Although once popularly touted as the “cuddle” or “love” hormone, the effects of OT are now well understood not to be universally prosocial, but instead highly contextual.<sup>217</sup> This is evident in current attempts to therapeutically administer OT. For example, a recent study

with school-aged children revealed no significant improvements in social behaviors, repetitive actions, or anxiety after 4 weeks of OT treatment compared to placebo. However, additional analysis showed that children who received OT in combination with structured psychosocial therapies experienced greater gains in social functioning than those treated with either approach alone. Outcomes were also influenced by parental expectations, with parents perceiving better results when they believed their child was receiving active treatment, particularly in the OT group. Notably, children who transitioned from placebo to OT during a follow-up phase demonstrated marked improvements in social skills beyond what was observed with placebo alone.<sup>218</sup>

Similarly, recent research exploring OT's effects on brain activity highlights its contextual nature and complexity. For instance, one study investigated how OT influences neural responses to fear directed at oneself versus fear directed at others. While OT administration increased activity in the anterior cingulate cortex during self-focused fear, it reduced anterior insula activity during empathy-related conditions.<sup>219</sup> These findings challenge the assumption that OT universally enhances empathy or prosocial behavior, suggesting instead that its effects depend on situational and individual factors, such as the presence of familiar people or personal characteristics like gender and mental health. Even the effect on social behavior displayed by an individual upon NAL administration is highly dependent on whether they are in a distressed state.<sup>174</sup> This nuanced understanding underscores the importance of actively tailoring OT-based interventions to specific social and psychological contexts rather than viewing it as a one-size-fits-all empathy enhancer.

These findings suggest that the effectiveness of OT, and likely any combinatorial treatment of OT and NAL, may be amplified by embedding it within social interventions that promote interaction and communication. This is supported by a recent randomized, double-blind, placebo-controlled trial where intranasal OT was combined with applied behavior analysis (ABA) in children with ASD. Changes in autism severity (GARS-2) and social/behavioral functioning (SDQ) were assessed at baseline, post-treatment, and 6-week follow-up. Intranasal OT combined with ABA significantly reduced ASD index scores and stereotyped behaviors compared to placebo, as well as parent and teacher-reported scores.<sup>220</sup> In contrast, a different rigorous and well-designed clinical work involving children and adolescents with ASD who received either OT or a placebo for up to 24 weeks showed no measurable impact on social outcomes.<sup>221</sup> This result has been theorized to be due to the uncontrolled social context;<sup>216</sup> that is, OT by itself may be enhancing the salience of social signals in the brain but for both unfavorable experiences as well as positive ones, resulting in no net gain in social function.

## New tools

Recent advancements in neuroscience, particularly with tools like CRISPR, DREADDs (designer receptors exclusively activated by designer drugs), and custom ligand design, hold promise for overcoming

ing challenges in targeted OT and  $\mu$ -opioid receptor modulation to enhance social behavior therapeutically. Each of these technologies allows unprecedented control over specific molecular and circuit-level targets, helping researchers to better understand the region-specific and temporal complexities of OT and opioid receptor activity in social behaviors.

CRISPR technology, particularly CRISPR-Cas9 and more refined versions like CRISPRa/CRISPRi, offers precise genome editing capabilities<sup>222</sup> that will allow researchers to manipulate the expression of OT and  $\mu$ -opioid receptors across different brain regions. By knocking out or upregulating OT receptor or  $\mu$ -opioid receptor genes in specific areas, CRISPR can help identify which neural circuits and receptor expressions are crucial for social behaviors, shedding light on how OT and NAL might be applied therapeutically without disrupting endogenous regulation. Moreover, CRISPR can assist in studying how variations in these receptor genes might affect sensitivity or response to therapeutic interventions, offering insights into patient-specific approaches. DREADDs provide a powerful method to manipulate specific neurons, using receptors that are only activated by synthetic ligands like clozapine-N-oxide.<sup>223</sup> Researchers can engineer DREADDs to respond specifically in OT receptor or  $\mu$ -opioid receptor-rich neurons, allowing control over OT and opioid receptor activity within targeted brain areas. This technology is particularly useful for studying spatial-temporal dynamics by allowing researchers to activate or inhibit certain pathways at different times, revealing how OT and opioids interact across regions in social behaviors and addressing therapeutic timing challenges.

Custom-designed ligands targeting OT or  $\mu$ -opioid receptors can enable more precise modulation of these receptors, minimizing off-target effects and maximizing therapeutic specificity. Such ligands can be engineered to preferentially activate or inhibit specific receptor subtypes, allowing researchers to dissect the individual contributions of OT and opioid pathways to social behaviors. Additionally, these ligands could be tuned to bypass peripheral barriers like the BBB, offering a potential solution to the challenge of limited central penetration for OT and enhancing its therapeutic efficacy.

Other emerging tools in neuroscience, such as optogenetics and single-cell RNA sequencing, further expand the toolkit for studying neuromodulatory pathways. Optogenetics allows researchers to control neuron activity with light, enabling real-time manipulation of OT receptor and  $\mu$ -opioid receptor-expressing neurons in animal models.<sup>224</sup> Single-cell RNA sequencing can reveal the expression profiles of these receptors across cell types and brain regions,<sup>225</sup> offering granular insights into how different neural populations contribute to social behavior. Together, these technologies promise to unravel the complexities of OT and opioid receptor interactions, potentially transforming therapeutic approaches for social behavior disorders.

## A path forward

Technologies such as optogenetics, CRISPR, and designer ligands offer unprecedented opportunities to decode and manipulate the oxytocin-

ergic and opioidergic systems in parallel with precision, paving the way for breakthroughs in treating deficits in social cognition. However, these interventions are still likely decades away from clinical adoption. Nonetheless, these enablers can be used in preclinical animal models to better elucidate the enormous complexities in the interplay between oxytocinergic and opioidergic systems and the best strategies to modulate these systems for enhancing social behaviors. Advanced therapeutics combined with appropriate contexts and behavioral interventions could unlock the potential of combined OT and NAL as a valuable tool for addressing social deficits.

## AUTHOR CONTRIBUTIONS

O.D.M. wrote the article, created the figure, and edited the manuscript. P.G. wrote the article. P.T.P. wrote the article and edited the manuscript. S.W.C.C. oversaw the project and wrote and edited the manuscript.

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## COMPETING INTERESTS

S.W.C.C. and O.D.M. are two of the inventors who hold a US patent, "Oxytocin and opioid antagonists for treatment of social dysfunction disorder," Patent no. 11160843, Application no. 16/398,744, issue date of 11/02/2021.

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