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REVIEW

# Acute and long-lasting effects of oxytocin in cortico-limbic circuits: consequences for fear recall and extinction

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## Abstract

The extinction of conditioned fear responses entrains the formation of safe new memories to decrease those behavioral responses. The knowledge in neuronal mechanisms of extinction is fundamental in the treatment of anxiety and fear disorders. Interestingly, the use of pharmacological compounds that reduce anxiety and fear has been shown as a potent co-adjuvant in extinction therapy. However, the efficiency and mechanisms by which pharmacological compounds promote extinction of fear memories remains still largely unknown and would benefit from a validation based on functional neuronal circuits, and the neurotransmitters that modulate them. From this perspective, oxytocin receptor signaling, which has been shown in cortical and limbic areas to modulate numerous functions (Eliava et al. Neuron 89(6):1291-1304, 2016), among them fear and anxiety circuits, and to enhance the salience of social stimuli (Stoop Neuron 76(1):142-59, 2012), may offer an interesting perspective. Experiments in animals and humans suggest that oxytocin could be a promising pharmacological agent at adjusting memory consolidation to boost fear extinction. Additionally, it is possible that long-term changes in endogenous oxytocin signaling can also play a role in reducing expression of fear at different brain targets. In this review, we summarize the effects reported for oxytocin in cortico-limbic circuits and on fear behavior that are of relevance for the modulation and potential extinction of fear memories.

Keywords Fear extinction · Fear retrieval · Oxytocin · Central amygdala · Prefrontal cortex

Abbreviations

| | |
|---|---|
| ACC | Anterior cingulate cortex |
| AVP1a-R | Vasopressin receptor |
| BA | Basal amygdala |
| BLA | Basolateral amygdala |
| CBT | Cognitive behavioral therapy |
| CeA | Central amygdala |
| CeL | Centro-lateral amygdala |
| CeM | Centro-medial amygdala |
| CS | Conditioned stimulus |
| CSF | Cerebrospinal fluid |
| dmPFC | Dorso-medial prefrontal cortex |
| GABA | Gamma amino butyric acid |
| IL | Infralimbic cortex |
| ITCd | Intercalated cell masses (dorsal) |
| ITCv | Intercalated cell masses (ventral) |
| LA | Lateral amygdala |
| NMDAR | N-methyl-d-aspartate receptor |
| Nacc | Nucleus accumbens |
| OT | Oxytocin |
| OTR | Oxytocin receptor |
| PKCδ | Protein kinase delta |
| PL | Prelimbic cortex |
| PTSD | Posttraumatic stress disorder |
| PVN | Paraventricular nucleus of the hypothalamus |
| US | Unconditioned stimulus |
| vmPFC | Ventromedial prefrontal cortex |

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## Introduction

Anxiety-related disorders are at present a worldwide psychiatric, pharmacological, and economical issue, and according to the World Health Organization (WHO 2016), since 1990, the number of people suffering from anxiety increased by nearly 50%. In fact, close to 10% of the world's population

is affected by mental disorders and this accounts for 30% of the global non-fatal disease burden (World Health Organization 2016). Thus, reducing anxiety and fear-related neuropathologies represents a priority in the current health system.

Fear memories are caused by concrete threats. During fear-conditioned learning, an aversive stimulus or unconditioned stimulus (US), like a mild electric foot shock in rodents or gunfire in humans, is associated with a neutral sensory stimulus or conditioned stimulus (CS), like a tone, a smell or a visual cue, resulting in the creation of a conditioned fear memory. When the individual is re-exposed to the CS, the fear memory is retrieved or recalled, generating a fear response, for example, freezing in rats and mice (LeDoux 2000; Alberini 2013), or fear-potentiated startle (often measured in humans) accompanied by the activation of a whole series of physiological responses (Debiec and LeDoux 2006; Quirk and Mueller 2008; Do-Monte et al. 2015). Meanwhile, anxiety states can be induced by circumstantial, potential, imagined, or anticipated threats, which are more related with the unspecific generalization of fear. Anxiety states and fear memories are brought about in part by the same neuronal circuits, involving the different subnuclei of the amygdala and the prefrontal cortex (LeDoux 2000, 2014; Davis et al. 2010; Tye and Deisseroth 2012; Anderson and Adolphs 2014; Tovote et al. 2015), so that treatment options of conditioned fear and anxiety can overlap. Furthermore, anxiety and fear memories are encoded in an ʙengram,^ which has been represented by a specific population of neurons activated during specific learning events (Tonegawa et al. 2015). This notion provides a cellular substrate that can be subjected to modulation during the recall of the original memory, but also during its extinction. Efficient therapies at modulating engrams to promote fear extinction are therefore needed, and extinction learning is at the basis of this. Indeed, extinction of conditioned fear responses, which encompasses the formation of new memories encoding safety, and thereby inhibiting fear, represents an important mechanism in the treatment of anxiety disorders, such as posttraumatic stress disorder (PTSD), social phobia, panic disorders, and fear generalization. In psychiatry, extinction training is commonly used in cognitive behavioral therapies (CBT) (Cisler et al. 2016; Klumpp et al. 2017; Abramowitz 2013). CBT focuses on identifying and modifying maladaptive patterns of conditioned behavior and is one of the most established methods to reduce fear (Stewart and Chambless 2009). In addition, it targets the neuronal processes that inhibit fear retrieval (Straub et al. 2017; Carpenter et al. 2018).

Extinction training involves repeated presentation of the CS in the absence of the US, and results in a diminished fear response towards the CS (Hofmann et al. 2015; Pavlov 1927; Alberini 2013). This is presumed to be the result of a cascade of genetic, molecular, and cellular changes (Myers and Davis 2007; Orsini and Maren 2012) that alter synaptic efficacy and neuronal network interactions in the pathways for retrieval and extinction of fear memories (Pape and Paré 2010; Tonegawa et al. 2015). The strength of extinction memory (extinction consolidation) is evaluated after the training, in so-called ʙextinction retrieval^ sessions, in which the conditioned fear is decreased, and therefore, also the potential anxiety that accompanies the fear memory is diminished (Quirk et al. 2006; Schiller et al. 2013). Extinction training, although effective in decreasing the fear response in the short term, does not erase the original fear memory trace, but forms a new, distinct memory (Milad and Quirk 2002; Quirk et al. 2006; Schiller et al. 2013; Kroes et al. 2016; Rashid et al. 2016). As a result, the original conditioned fear response can reoccur with time through spontaneous recovery, reinstatement, and renewal (Rescorla 2004; Kim and Richardson 2010). Remarkably, the extinction memory does not generalize as easily to new contexts, as the original conditioned fear memory does during anxiety states (Woods and Bouton 2006). Because extinction learning does not generalize to situations outside the extinction context, it is therefore not the best clinical tool for long-lasting fear reduction.

A different method to reduce the fear response is the use of pharmacological agents that target precisely the synaptic plasticity of neuronal circuits of extinction memories, whose downstream signaling pathways can allow fear extinction and strengthen extinction memory unremittingly in preclinical and clinical models (for extensive review follow: Bukalo et al. 2014; Singewald et al. 2015). Indeed, pharmacological agents applied after retrieval of the fear memory might facilitate fear extinction, as evidenced by the apparent amnesic effects of propranolol, a beta-adrenergic antagonist, in animals and humans (Kroes et al. 2016; Giustino et al. 2016). Although propanolol has been accepted as a clinical option for general anxiety, its precise mechanism lies in the amnesic effect on retrieved fear memories, and are not fully validated in the circuits for fear extinction (Debiec and Ledoux 2004; Steenen et al. 2016). In the same line, the antibiotics anisomycin (a blocker of protein synthesis) and d-cycloserine (partial NMDA receptor agonist that works as a cognitive enhancer) seem to support fear extinction as well (Nader et al. 2000; Ledgerwood et al. 2005; Anderson and Insel 2006; Hofmann et al. 2015; Bowers and Ressler 2015a, 2015b). While the use of anisomycin is limited by its high toxicity, as it blocks all protein synthesis, d-cycloserine is already being used in combination with CBT to enhance fear extinction. On one hand, it is thought to suppress the initial fear memory, and on the other hand to promote extinction learning through activation of NMDA receptors (Davis et al. 2006; Bowers and Ressler 2015b; Mataix-Cols et al. 2017; Goodman et al. 2018).

Although these examples show the beneficial effects of pharmacological agents, as co-adjuvants of extinction

therapies, some other reports suggest that co-adjuvant use of anxiolytics provides only modest gains in fear extinction or can even impair extinction learning working by acting as potential anxiogenics (Singewald et al. 2015). An example of this can be found in positive allosteric modulation of $GABA_A$ receptor activity via the benzodiazepine-binding site (Clark et al. 2004; Knoflach et al. 2016; Duke et al. 2018). Because of the sedating and calming effects of benzodiazepines, they might in fact hinder extinction via reduced arousal and decreased release of noradrenaline and glucocorticoids, neuromodulators that support extinction (Otto et al. 2005; Bentz et al. 2010). Similar concerns have been raised for the use of serotonin selective reuptake inhibitors (SSRI). Chronic treatment with some SSRIs (e.g., fluoxetine) but not all (e.g., citalopram) enhances extinction in rodents (Burghardt and Bauer 2013). However, acute SSRI treatment could on the other hand induce anxiogenic effects (Campbell and Merchant 2003; Salchner and Singewald 2006). Finally, another interesting compound is venlafaxine, a combined 5-HT and noradrenaline reuptake inhibitor with weaker affinity for the noradrenaline transporter (Owens et al. 1997). This compound improves extinction retrieval and protects against fear reinstatement in rodents (Yang et al. 2012). In summary, some pharmacological compounds could target the brain networks responsible for fear extinction but in a rather unspecific manner. A more effective and innocuous pharmacological approach should therefore be adopted to specifically target the consolidation and reconsolidation of extinction memories (Alberini 2013) (Fig. 1).

Here, we discuss the neuropeptide oxytocin (OT) as a potential endogenous regulator of the neuronal plasticity behind fear expression and extinction-related behaviors, and which can easily be applied intranasally to improve fear extinction learning in humans (Eckstein et al. 2015, 2017). Oxytocin is a well-established anxiolytic when exogenously applied or endogenously released in several brain regions, including the PVN where it is synthesized (Blume et al. 2008; Jurek et al. 2012). In this area, its anxiolytic activity is brought about by the recruitment of an oxytocin receptor (OTR)−TRPV2 channels (and subsequent Ca2+ influx)−MEK1/2 pathway (van den Burg et al. 2015). Underlying mechanisms of oxytocin and fear extinction in other brain regions, like the PFC and amygdala, are beginning to be explored, motivated by the discovery of OT release and OTR expression in those areas (Knobloch et al. 2012; Mitre et al. 2016; Li et al. 2016; Rogers et al. 2018).

## Cortico-limbic circuits for fear retrieval and extinction memories

As the modern standpoint in psychiatry pursues a more precise circuit-based therapy, a pertinent pharmacological methodology must target the neuronal populations, where extinction memories are formed and consolidated (Fitzgerald et al. 2014; Bukalo et al. 2014). The circuits between the prefrontal cortex and the amygdala represent the physiological substrate for the recall or retrieval of fear memories, but also extinction memories (Fig. 1). Moreover, these brain areas express the receptor for oxytocin (OTR). Thus, the physiological interactions between the brain areas involved, as well as the neuromodulators such as OT that regulate their functions, represent a clear anatomical substrate to facilitate strengthening of fear extinction memories.

### Amygdala

In the classical circuit model of fear conditioning, the lateral nucleus of the amygdala (LA) is the primary site where associations between the CS and the US are formed and stored (Davis 1992; LeDoux 2000; Maren 2001). LA pyramidal neurons project to the central nucleus of the amygdala (CeA), which then mediates the physiological and behavioral expression of conditioned fear responses. CeA output neurons, most of which are located in its medial subdivision (CeM), project to downstream targets in the brainstem and hypothalamus that orchestrate conditioned autonomic and motor responses (Krettek and Price 1978; Veening et al. 1984; LeDoux et al. 1988). Nevertheless, circuits within the CeA have also been shown to be important for acquisition as well as expression of fear (Ciocchi et al. 2010; Haubensak et al. 2010; Duvarci et al. 2011; Amano et al. 2012; Li et al. 2013a).

In these different studies, distinct cell types have been identified based on functional and genetic criteria. In the lateral subdivision of CeA (CeL), $PKC\delta^+$ mRNA-containing neurons exhibit inhibitory CS responses, also called $CeL_{OFF}$ cells. These $PKC\delta^+$ neurons receive local inhibitory inputs from CS-activated $PKC\delta^-$ neurons ($CeL_{ON}$), and in turn make inhibitory synaptic contacts with PAG-projecting CeA output neurons, thereby gating acute CeA output through disinhibition. CeM output cells are under tight inhibitory control of this GABAergic microcircuit located in the CeL. This microcircuit can be activated by OT, resulting in inhibition of neuronal activity in the CeM (Cassell 1999; Huber et al. 2005; Ehrlich et al. 2009; Viviani et al. 2011; Knobloch et al. 2012).

Abbreviations: ACC, anterior cingulate cortex; PL, prelimbic cortex; IL, infralimbic cortex; LA, lateral amygdala; BA, basal amygdala; ITCd, intercalated cells dorsal; ITCv, intercalated cells ventral; CeL, centro-lateral amygdala; CeM, centro-medial amygdala; PAG, periaqueducal gray

While this anatomical arrangement is at the basis of the physiological and behavioral expression of fear, recent studies have highlighted that the microcircuitry in the CeA is important for fear memory as well. For example, during fear retrieval and accompanying freezing behavior, excitatory synapses onto somatostatin-positive neurons ($CeL_{ON}$) in the CeL

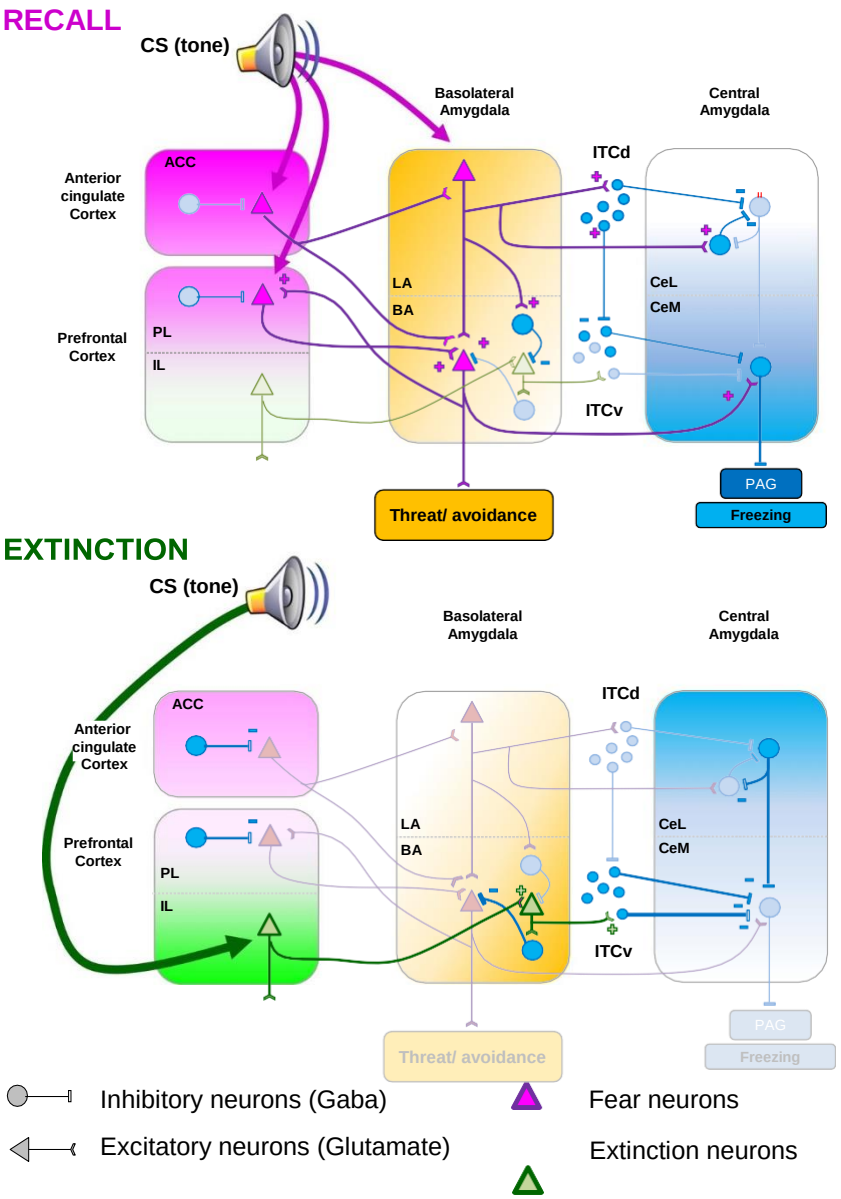


Figure 1 Hypothetical circuits involved in recall and extinction of fear memories. In this hypothesis, two parallel mechanisms are involved to induce the CS responsiveness of CeM output neurons after conditioning. The balance between excitatory inputs from BA and the inhibitory inputs from CeL and ITCv inputs to CeM triggered its CS responsiveness. This balance can be modulated by the ACC and prefrontal cortex (PL or IL) activities. Recall pathways (upper part of the panel): The CS-activated LA neurons projecting to BA neuron subtype (ʙfear neurons,^ pink triangle) to excite CeM cells, whereas another type of BA neurons (ʙextinction neurons,^ green triangle) are inhibited. The response from LA and BA ʙfear neurons^ can be modulated through excitatory interactions with each other and/or with prelimbic (PL) cells and anterior cingulate cortex, would reinforce the activity in LA during CS presentation. Conversely, the activation of LA neurons also leads to the recruitment of ITCd inhibitory cells and of a subgroup of CeL interneurons named $CeL_{On}$/PKCδ-. ITCd neurons would then inhibit ITCv cells, disinhibiting CeM neurons. In addition, ITCd cells would inhibit another subgroups of CeL interneurons named $CeL_{Off}$/PKCδ+. These activations cause a further inhibition of PKCδ+ neurons and disinhibition of CeM cells leading to freezing response. These mechanisms take place only when the threat is inescapable, otherwise the neurons from BA lead to escape behavior. Extinction pathways (lower part of the panel): These balance between two parallel mechanisms leads to the decrease of fear response to the CS presentation and the activation of CeM output neurons during extinction. During this new phase of learning, the CS diminished rapidly the recruitment of BA ʙfear^ neurons leading to a disinhibitions of BA ʙExtinction^ neurons (green). Moreover, the projections from Infralimbic to BA (and reciprocally) might also enhance the excitability of BA ʙExtinction^ cells. The disinhibition of extinction cells induced the activation of a subgroup of interneurons in BA inhibiting ʙfear^ neurons. In parallel, the reduction of activity in LA causes a disaffiliation of ITCd neurons leading to an activation by disinhibition of ITCv neurons, and simultaneous activation by BA 'Extinction' glutamatergic neurons. Moreover, the subsets of CeL cells PKCδ+ can be disinhibited leading to the inactivation of CeM neurons and less fear responses.

experience a robust synaptic potentiation (Li et al. 2013a, b). Additionally, optogenetic stimulation of basolateral amygdala (BLA) terminals in the CeA results in anxiolysis during the retrieval of fear context (Tye et al. 2011), possibly brought about by activation of $CeL_{OFF}$ cells expressing the OTR (Haubensak et al. 2010; Viviani et al. 2011). Thus, the observed changes in plasticity (the cellular correlate of learning) and bidirectional modulation of fear-related behavior through $CeL_{ON}$ and $CeL_{OFF}$ cell activity establish the CeA as an important node in the expression of fear, and a locus for fear memory.

Another relevant mechanism for extinction involves the activation of the intercalated cell masses (ITC) of the amygdala (Royer et al. 1999; Quirk et al. 2003; Paré et al. 2004; Amano et al. 2010; Amir et al. 2011; Bukalo et al. 2014). The ITCs include clusters of tightly packed, GABAergic neurons connected with the fiber bundles that lie between the BA/LA and the CeL/CeM nuclei. Further reports have highlighted the heterogeneity of diverse ITCs. The dorsal and ventral ITC nuclei are heavily interconnected, exhibit miscellaneous electrophysiological and molecular profiles, and are differentially activated by fear and fear extinction, while dorsal ITC activity emerge during fear recall, ventral ITC activity is enhanced during fear extinction (Geracitano et al. 2007; Kaoru et al. 2010; Busti et al. 2011; Bukalo et al. 2014). In fact, general excitatory synaptic signaling onto the ventral ITC population appears to be necessary for fear extinction, as a mouse model lacking the serine protease inhibitor protease-nexin-1 (PN-1), that modulates NMDAR-mediated synaptic currents in the vITC, displays impaired fear extinction (Meins et al. 2010).

### Prelimbic versus infralimbic cortices

The fundamental role of the prefrontal cortex to retrieve, consolidate, and extinguish fear memories has been well-demonstrated in a plethora of pharmacological, optogenetic, and electrophysiological studies. These roles seem to be conserved between rodents and humans, and homologous subnuclei in the prefrontal cortex have been found in both species (Fig. 2). In rodents, the subnuclei are named, from dorsal to ventral: anterior cingulate cortex (ACC), prelimbic cortex (PL), and infralimbic cortex (IL). They correspond respectively to the human anterior cingulate cortex (ACC), dorso-medial prefrontal cortex (dmPFC), and ventro-medial prefrontal cortex (vmPFC) (Milad et al. 2006; Quirk and Milad 2010; Likhtik et al. 2014; Duvarci and Pare 2014; Giustino and Maren 2015).

The PL and IL play opposing roles in encoding fear memories, triggering fear retrieval, and fear extinction, respectively (Vidal-Gonzalez et al. 2006; Herry et al. 2008; Quirk and Milad 2010; Milad and Quirk 2012; Little and Carter 2013; Courtin et al. 2014; Senn et al. 2014; Dejean et al. 2016; Karalis et al. 2016; McGarry and Carter 2017). This difference is due to the differential functional connectivity patterns of PL and IL with unique populations of pyramidal cells in the BLA, and is amplified by mutual inhibition driven by interneuron populations in both prefrontal subnuclei (Vogel et al. 2016; Bukalo et al. 2015; Vertes 2004; Vidal-Gonzalez et al. 2006; Cho et al. 2013; Courtin et al. 2014; Saffari et al. 2016; Karalis et al. 2016). The BLA pyramidal neurons project back to both the PL and IL sub regions, creating a feedback loop (Gabbott et al. 2006; Hoover and Vertes 2007; Senn et al. 2014; Burgos-Robles et al. 2017; McGarry and Carter 2017). These BLA inputs to the PL and IL modulate the excitatory/inhibitory balance on cortical pyramidal cells, possibly via engagement of local interneurons (Ishikawa and Nakamura 2003; Sun and Laviolette 2012; Sotres-Bayon et al. 2012; Dilgen et al. 2013). Then, the bidirectional projections between PL/IL and the BLA encode the experience-dependent retrieval versus extinction processing of fear memories by balancing PL vs. IL activity.

### Anterior cingulate cortex

Besides the PL and IL, the anterior cingulated cortex (ACC) also sends projections to the BLA, and modulates the expression and retrieval of fear (Vertes 2004; Sierra et al. 2017; Webb et al. 2017; Yin et al. 2018). In rodents, this area is responsible for the enhancement of contextual fear generalization after fear conditioning, and for the transfer of socially derived fear through its connections with the amygdala (Cullen et al. 2015; Pisansky et al. 2017; Allsop et al. 2018). In humans, local GABAergic signaling in the ACC promotes fear extinction, which suggests that inhibition of the dorsal ACC may initially inhibit the retrieval of fear memories, and thus facilitates extinction learning (Levar et al. 2017a, 2017b).

Additionally, some structural and functional deficits in this area have been found in fMRI studies in neuropsychiatric disorders, such as generalized anxiety disorder (Andreescu et al. 2017) and PTSD (Shvil et al. 2014), which both affect severely the extinction of fear memories. In the case of PTSD, interestingly, the activation of ACC, together with the vmPFC and hippocampus, is sexually dimorphic: men with PTSD exhibited increased activation in the left rostral dACC during extinction recall compared to women with PTSD (Shvil et al. 2014; Yoon et al. 2017). Further, animal and human studies (Cullen et al. 2015; Levar et al. 2017a, 2017b) have positioned the ACC as an important hub to trigger fear retrieval alongside the PL, and its inhibition might be a way to boost fear extinction.

## Modulation of fear circuits by oxytocin in preclinical animal models

### Rodents

There is quite a lot of evidence that OT acts in different brain areas to decrease anxiety responses and conditioned fear

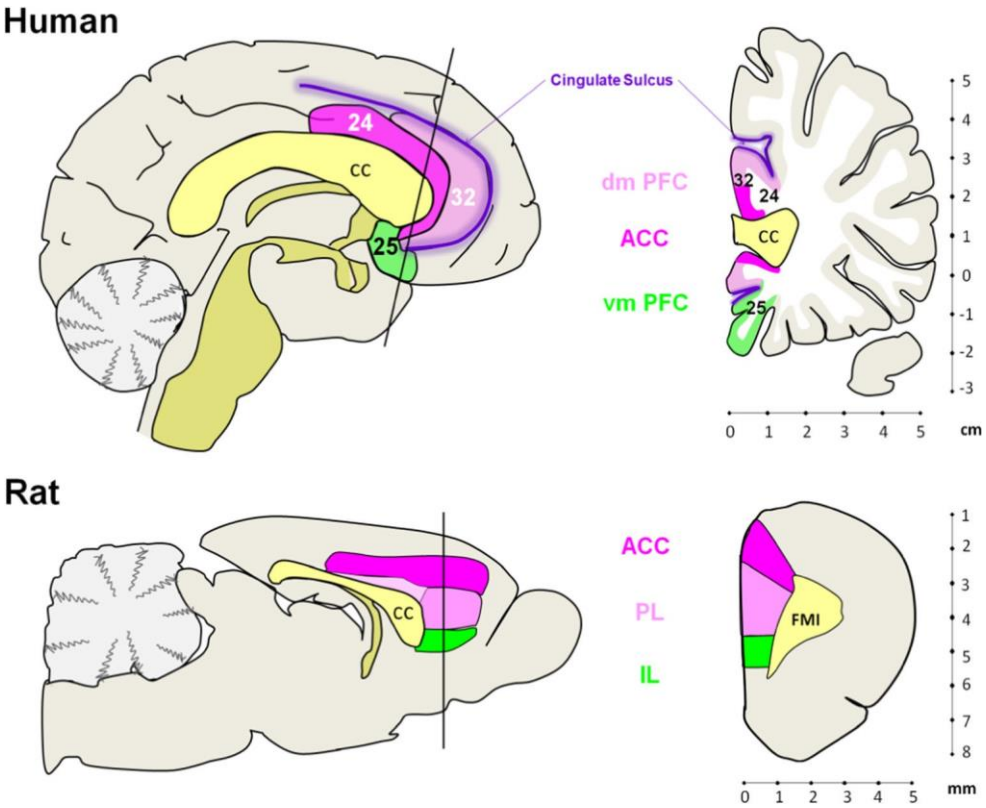


Fig. 2 Anatomical locations of the anterior cingulate cortex (ACC), prelimbic (PL), and infralimbic (IL) subregions of the medial PFC, showing equivalence between the human and rat brains. The rodent PL region is largely associated to Brodmann area 32, while the IL is analogous to Brodmann area 25. The ACC is mainly associated with the Brodmann area 24. Usually these observations are based on the different type of thalamic inputs to these regions

responses during retrieval in rodents (Fig. 3). Indeed, OTRs- and OT-binding sites have been found in those circuits, especially in the ACC, PL, and CeL (Huber et al. 2005; Nakajima et al. 2014; Burkett et al. 2016; Li et al. 2016; Sabihi et al. 2017) (Jiménez et al. 2015), that together constitute the fear retrieval network. The OTRs are expressed specifically by GABAergic interneurons in all of the brain regions involved in fear retrieval (Huber et al. 2005; Owen et al. 2013; Nakajima et al. 2014; Marlin et al. 2015; Sabihi et al. 2017). Importantly, OT-positive fibers originating from the PVN project to these areas (Knobloch et al. 2012), and, at least in the CeL, OT is released from these fibers as observed following optogenetic stimulation and application of an OTR antagonist. Furthermore, OT release in the CeL is sufficient to decrease conditioned fear responses, clearly demonstrating the anxiolytic potential of OT in a pathway that mediates fear retrieval when the animals are re-exposed to the conditioned fear context. It has further been shown that the OTR mRNA is indeed present in part of the $CeL_{OFF}$ cells in the CeL (Haubensak et al. 2010), and we found that activation of these receptors inhibits the CeM and its output to downstream effector regions (Huber et al. 2005; Viviani et al. 2011; Knobloch et al. 2012). Furthermore, the OTR has been found in the basolateral amygdala (BLA), another hub for extinction memories, by means of immunohistochemistry and autoradiography (Stamatakis et al. 2016; Mitre et al. 2016). In fact, it has been suggested that the extinction of conditioned fear is facilitated by local infusions of OT or TGOT (specific agonist of the OTR) in the BLA, but not in the CeA (Campbell-Smith et al. 2015).

By using an OTR antagonist, it has further been shown that endogenous OT has similar anxiolytic effects in the PL, as it has in the CeL (Nakajima et al. 2014; Li et al. 2016; Sabihi et al. 2017). In addition, optogenetic and pharmacological activation of the OTR in the PL reduces anxiety-like behavior, in a gender-dependent manner (Li et al. 2016), further characterizing the differential role of different prefrontal-amygdala circuits during the modulation of fear memories in female and male rodents (Shansky et al. 2010; Gruene et al. 2015). Moreover, Mitre et al. (2016) found a higher density of the OTR expression within the PL of lactating females compared to virgins or males rodents. Consistent with this, Sabihi et al. (Sabihi et al. 2014) showed that blocking the OTR in this area enhances anxiety in lactating but not virgin females. In addition, in the ACC, the OTR is also expressed (Mitre et al. 2016), and an OTR antagonist infused into this region abolished the partner-directed consolation behavior during fear transfer in prairie voles (Burkett et al. 2016).

While OT can exert acute anxiolytic effects by reducing the activity of the fear retrieval network, especially in the central amygdala (Fig. 3), it might also modulate plasticity of the fear extinction network to bring about the reduction of fear responses. This would require the presence of OTRs for instance in the IL, or inhibitory actions in the PL or ACC (as in the CeA). Indeed, administration of OT in the IL of fear-

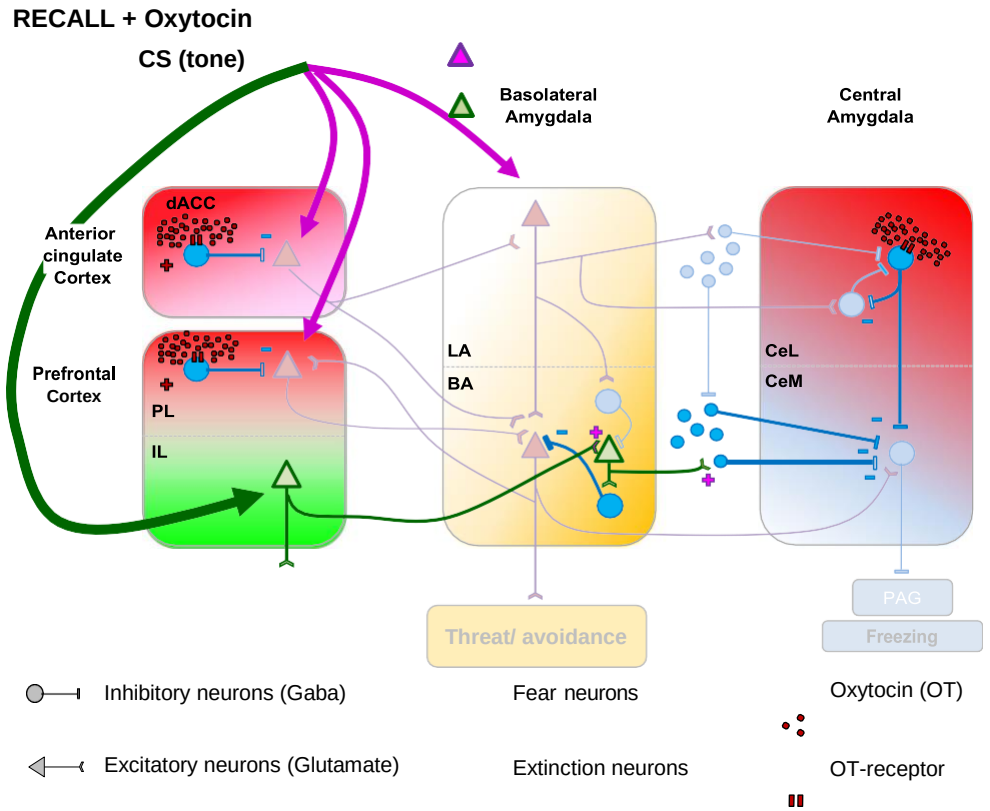


Fig. 3 Modulation by oxytocin signaling of the balance between fear recall and fear extinction. In this hypothesis, oxytocin would allow a switch from fear recall to fear extinction, based on the hypothetical model of circuitry presented in Fig. 1. This model revealed a complex mechanism involving always a balance between inhibition and excitation leading to increase or decrease the CS responsiveness from CeM neurons. In oxytocin model of switching fear to extinction, the presence of oxytocin would activate the receptors localized only on the interneurons of ACC, PL, and CeL. Interestingly, in CeL the OT-receptors are only on cell PKCδ+. During the recall, the CS activated LA neurons projecting to BA neuron subtype (ʙfear neurons,^ pink triangle) to excite CeM cells, whereas another type of BA neurons (ʙextinction neurons,^ green triangle) are inhibited. Oxytocin receptors are localized on interneurons of regions (ACC, PL, CeL) involved in recall, thus the activation of these receptors by oxytocin leads to inhibit the ʙfear^ neurons and to recruit more ʙextinction^ neurons in BA. Oxytocin would diminish rapidly the capacity from the CS to recruit ʙfear^ neurons in BA leading to a disinhibition of BA ʙextinction^ neurons (green). Moreover, the projections from infralimbic to BA (and reciprocally) might also enhance the excitability of BA ʙextinction^ cells. The disinhibition of extinction cells induced the activation of a subgroup of interneurons in BA inhibiting ʙfear^ neurons. In parallel, the reduction of activity in LA causes a disaffiliation of ITCd neurons leading to an activation by disinhibition of ITCv neurons, and simultaneous activation by BA ʙextinction^ glutamatergic neurons. Moreover, the subsets of CeL cells PKCδ+ can be disinhibited leading to the inactivation of CeM neurons and less fear responses. Abbreviations: ACC, anterior cingulate cortex; PL, prelimbic cortex; IL, infralimbic cortex; LA, lateral amygdala; BA, basal amygdala; ITCd, intercalated cells dorsal; ITCv, intercalated cells ventral; CeL, centro-lateral amygdala; CeM, centro-medial amygdala; PAG, periaqueducal gray

conditioned rats resulted in facilitation of subsequent extinction (Lahoud and Maroun 2013). Furthermore, social interaction during extinction training facilitates the consolidation of extinction, and this effect is mediated by the pharmacological manipulation of OTR signaling in IL (Brill-Maoz and Maroun 2016). However, interpretation of these observation is not as straight forward as one might think, as OTRs and OT-releasing fibers are absent in this region (Knobloch et al. 2012; Mitre et al. 2016). Nonetheless, a different study showed the presence of OTR-binding sites in IL of rats using autoradiography (Hansson et al. 2018).

## Non-human primates

While OTR expression has clearly been demonstrated in rodent brain regions involved in fear extinction and fear recall, this

seems to be different in non-human primates, since the identification of these receptors has certain technical limitations. Here, OTRs appear rather expressed in brain areas related to the integration of visual stimuli (Freeman et al. 2014; Freeman and Young 2016) that are upstream of the fear-controlling regions. For example, the nucleus basalis of Meynert (NBM) projects to the amygdala and it is the primary source of cholinergic input to the BLA (Nagai et al. 1982; Woolf and Butcher 1982). This cholinergic input is required for memory consolidation (Power et al. 2003), possibly promoting the oxytocin signaling-dependent encoding of memory during sustained attention to visual stimuli (Freeman and Young 2016), with relevance for social- and fear-related behaviors.

In chimpanzees, OT-immunoreactive fibers have been found in the ACC, but not in that of macaque monkeys (Rogers et al. 2018). In addition, OTRs seem to be completely

absent in these animals, and then OT is taken over by the closely related vasopressin receptor 1. Exogenous OT and AVP can bind to AVP receptors in the ACC of male macaques, with behavioral consequences (Jiang and Platt 2018), suggesting that exogenous OT may shape social and fear retrieval memories in primates via binding to AVP receptors (Terashima et al. 1999; Chini et al. 2008; Loyens et al. 2012). This finding supports the direct effect of OT in the CeA of different non-human primates, where the AVP receptors are densely expressed, but not the OTRs (Young and Flanagan-Cato 2012; Freeman et al. 2014).

## Modulation of fear circuits by oxytocin in humans

In humans, OTR-binding sites have been found in specific relays of the fear retrieval pathway in postmortem tissue. For example, Hansson et al. (2018) observed OTR expression by autoradiography in the ACC and Uhrig et al. (2016) also showed *OTR* mRNA and OT-binding sites in Brodmann area 10, which is part of the rostrolateral prefrontal cortex, and hence, of the fear retrieval pathway. Furthermore, as in the brain of chimpanzees, OT-positive fibers terminate in the ACC (Rogers et al. 2018), indicating a possible divergent evolution of the OT and AVP systems in more evolved primates. Taken together, it seems that OT signaling modulates the activity of fear retrieval and recall pathways across many species, including humans.

In humans, although the intranasal route of delivery does not allow for a precise targeting of brain regions (Leng and Ludwig 2016), it has been indeed the method of choice to deliver OT into the brain. Various key reports have even demonstrated that OT levels increase in the CSF after intranasal administration (Chang et al. 2012; Neumann et al. 2013; Striepens et al. 2013; Dal Monte et al. 2014; Modi et al. 2014). In fact, fMRI studies detail widespread changes in BOLD signals in the majority of brain regions expressing OTRs after this application, among which the amygdala subnuclei (Gamer et al. 2010; Paloyelis et al. 2016). Some of these fMRI studies highlight the anxiolytic effects, with a locus in brain areas and subnuclei that belong to the fear retrieval circuit after intranasal administration of OT (Gamer et al. 2010). As in rodents, OT has general anxiolytic acute properties in humans, decreasing the reactivity of the amygdala to fearful faces (Kirsch et al. 2005; Domes et al. 2007; Labuschagne et al. 2010). Noteworthy, intranasal administration of OT can promote differential behavioral outcomes in men and women, in terms of emotional salience (Domes et al. 2010; Rilling et al. 2014; Luo et al. 2017). Interestingly, in the ACC, activation of the dorsal part in response to fearful faces is diminished following intranasal OT application in men, but increased in women (Luo et al. 2017), indicating a sex-dependent outcome of OT modulation in fear retrieval. This sexual dimorphism in cortical oxytocin signaling resembles that observed in the PL of mice (Li et al. 2016). Similarly, different reports show that while OT decreases amygdala reactivity to threatening faces in men, it rather enhances the same amygdala reactivity to similar threatening faces in women, when they are in the luteal phase of the menstrual cycle (Domes et al. 2010; Lischke et al. 2012). This observation suggests a sex-specific difference in OT-dependent threat processing. It is potentially due to the interaction of OTR with gonadal steroids, such as progesterone and estradiol, which have a more pronounced impact in the female brain. Adding to this idea, intranasal OT shows sex-specific functional roles via the amygdala to enhance the salience and attractiveness of positive social attributes in women but enhancing the salience of the negative ones in men (Gao et al. 2016). This is a behavioral and functional proof of how this molecule's network could have evolved in a different way in men and women, in order to display social relations and threat responses.

These studies support the idea that OTR signaling can be sex-dependent in the modulation of fear circuits, and that its role to enhance the sensitivity to salient social stimuli can be affected by sex-dependent networks, like the gonadal steroid hormones. Importantly, steroid hormones, such as estradiol and progesterone have been found to modulate the OTR: estradiol enhances OTR affinity for OT, while progesterone decreases receptor binding (Gimpl et al. 2002; Choleris et al. 2008). These hormones regulate synaptic plasticity, NMDAR function and LTP, fundamental effectors of learning and memory (Milad et al. 2009; Gillies and McArthur 2010; Shansky et al. 2010; Zeidan et al. 2011; Milad and Quirk 2012). Such gender difference might also be quite relevant for psychiatric conditions related with disrupted fear extinction, like PTSD, that are more prevalent in women than in men (Kessler et al. 2017; Ramikie and Ressler 2018). Therefore, when applying OT in humans, it is important to consider these gender differences, and this also applies to preclinical research in animal models, where these differences have not either been consistently addressed.

While research in rodents has clarified many aspects of acute anxiolytic actions of OT, and of the inhibition of fear retrieval by OT signaling, research in humans has been much more ambivalent. Besides potential differences in the way the induced behavioral and emotional changes are interpreted, this may also be due to the different methods of OT administration (Leng and Ludwig 2016; Walum et al. 2016). Indeed, human studies typically administrate oxytocin itself by intranasal application route. As a result, in these studies, OT may also reach vasopressin receptors through which it is known to often exert opposite effects, e.g., in the amygdala (Huber et al. 2005). Animal studies, in contrast, often apply the much more specific OTR agonist Thr4Gly7-OT (TGOT), or the specific OTR

agonist (OTA) and target these compounds through local injection to the brain regions under study.

Nonetheless, in fear extinction procedures, intranasal OT after Pavlovian fear conditioning of healthy subjects increases electrodermal responses and vmPFC signals to conditioned fear in the early phase, and decreases amygdala activity in the late phase of extinction (Eckstein et al. 2015). Similarly, intranasal OT promotes recall of fear extinction up to 24 h after fear extinction training (Acheson et al. 2013). To promote the consolidation of fear extinction, OT administered in men inhibits amygdala responses to negative stimuli, and facilitates left insula responses for subsequent memory retrieval (Striepens et al. 2012), to form a memory of aversive social stimuli (Striepens et al. 2012). This is a very fascinating discov- ery that has not been found before in animals and postu- lates that OT could have long-lasting effects in memory consolidation for socially aversive cues. In addition, Eckstein and colleagues showed that exogenous OT increases the functional connectivity of the BLA with the dmPFC, and decreases that of the CeM, output region of the amygdala for negative emotional salience (Eckstein et al. 2017). Together, these examples show that OT could modulate memory consolidation to boost fear extinction in a long-lasting manner. This makes OT a promising pharmacological agent for the treatment of fear and anx- iety disorders.

However, surprisingly, exogenous administration of OT in humans can also have contrasting effects (MacDonald et al. 2013), for example, facilitating Pavlovian fear learning, correlated with heightened activity in ACC (Eckstein et al. 2016). Moreover, in experimental designs using unpredictable threats, OT promotes anxiogenic effects by enhancing the potentiated startle reflex (Grillon et al. 2013). This could be explained from the functional role of OT to bind and stimulate the BNST (Moaddab and Dabrowska 2017; Dabrowska et al. 2011; Knobloch et al. 2012; Martinon and Dabrowska 2018; Duque-Wilckens et al. 2018), a structure that underlies sustained anxiety-like behaviors to uncertainty by directly activating corticotrophin releasing factor neurons. A better understanding of the consequences of OT administration in different brain areas, and in diverse social and non-social contexts, as well as a fully characterization of the dose-response function in clinical studies is warranted. Moreover, although current data supports the inhibition of cortico-amygdaloid retrieval circuits by exogenous OT applications, more knowledge about the specific cell types or synaptic modulations in those networks are required, for example, in a clinical setting, through a PET scan that could screen OT tonic activity in the brain, as it exists for the dopaminergic signaling (Volkow et al. 2005). Indeed, there have recent efforts to develop radioligands of OT that can be used for monitoring OT receptor distribution in humans (Smith et al. 2016a).

## Oxytocin treatment: mode of action

In addition to acting as an acute anxiolytic to diminish fear responses, mainly in the CeA and other areas (Litvin et al. 2016; Viviani et al. 2011; de la Mora et al. 2016; Sabihi et al. 2017; Grund et al. 2017; Menon et al. 2018), OTcould also act on fear learning, and fear extinction learning in a long-lasting manner. In other words, it could work on neuronal plasticity in the fear-related neural networks. Unfortunately, studies describing the mechanism of OT on synaptic plasticity in the ACC, PL, IL, BLA, and CeL are still scarce. However, a recent report demonstrated that, while intranasal acute administration of OT increases cellular activity in ACC and correlated with the transfer of socially derived fear, as in Burkett et al. 2016, chronic administration of OT had similar behavioral effects that correlated with decreased OTR mRNA in the CeA (Pisansky et al. 2017). Considering that intranasal OT could also affect VP receptors, these findings should be interesting to consider in light of the opposite effects both receptors exert in the CeA on expression of fear (Huber et al. 2005).

Furthermore, OT signaling in other brain areas brings about plastic synaptic changes that rely on the OTR (Fang et al. 2008). For example, in the nucleus accumbens, OT acts presynaptically to induce long-term depression (LTD), which has been associated with social reward (Dölen et al. 2013; Gur et al. 2014; Marlin et al. 2015; Mitre et al. 2016). Likewise, in the medial amygdala, OT induces LTD, which is fundamental for social recognition (Gur et al. 2014). Finally, OT has been shown to promote long-term potentiation in the auditory cortex in response to vocal calls of the pups (Marlin et al. 2015; Mitre et al. 2016) and in the hippocampus of lactating mothers through activation of MEK1/2 and CREB to improve spatial learning (Tomizawa et al. 2003). Taken the results of these studies together, it appears that OT can induce plastic changes in social contexts, in line with its proposed pro-social dynamic function (Fang et al. 2008; Marlin et al. 2015; Stoop et al. 2015; Modi et al. 2015; Coria-Avila et al. 2014; Triana-Del Rio et al. 2015). Therefore, we propose that putative contributions of OT to neuronal plasticity in the fear retrieval and extinction circuits can be best studied in relation to social interactions. In agreement with this, OT is released in the CeA in lactating mother rats in the presence of their pups (i.e., a social stimulus) to reduce freezing and increase active defensive behavior to protect the pups (Rickenbacher et al. 2017). The proof of whether OT release under socially relevant conditions induces plastic changes in the circuits of fear extinction is thus an attractive question waiting to be answered.

Finally, at the clinical level, OT has successfully been used to treat PTSD, having an acute anxiolytic effect, but only in those patients with less severe symptoms (Sack et al. 2017). Anxiolysis might be explained here by restoration of the

pathologically low OT endogenous brain concentration in those patients (Donadon et al. 2018). At the circuit level, it thus appears that the increased release of endogenous OT from the PVN can activate different inhibitory neuronal populations in the brain expressing the OTR, that collaborate all together to diminish conditioned fear responses and anxiety during retrieval and, simultaneously, allow for extinction of fear memories in a ʙsocial^ context-dependent modulatory manner.

Conclusion and perspectives

Recent research has not only established OT as an acute anxiolytic, but also as a modulator of long-lasting synaptic plasticity, especially in social contexts. This makes possible to combine OT with cognitive behavioral therapy for the treatment of anxiety disorders and trauma. However, the precise contribution of OT to fear extinction learning is hard to distinguish from its anxiolytic effects. This is partially due to almost a unique behavioral readout to evaluate fear responses in animal studies (freezing), and the experimental need to look for other outcomes (Blanchard et al. 1991; Myers and Davis 2007; Hegoburu et al. 2011; Wöhr and Schwarting 2013). For instance, we have found that, although OT does decrease freezing when released in the CeA, it is without effect on other parameters of fear, especially heart rate variability (Viviani et al. 2011). Instead, OT might induce a switch from passive to active defensive behavior as demonstrated in lactating mothers (Bosch et al. 2005; Rickenbacher et al. 2017), in the presence of social stimuli. Thus, there is still a lot to be discovered about the role of OT in anxiety-like behavior, not in the least about plastic long-lasting changes in the corticolimbic fear memory circuits.

Altogether, taking in consideration its region-specific and sex-specific effects, OT presents itself as a candidate molecule to facilitate fear extinction and anxiolysis, with the advantages that it is easy to apply, is endogenous, and its potential use is based on well-characterized neural circuitry controlling fear and anxiety responses, in animal models as well as in humans.

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