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Why is running a marathon like giving birth? The possible role of oxytocin in the underestimation of the memory of pain induced by labor and intense exercise

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ABSTRACT

Pain can be overestimated, underestimated or reported accurately at recall. The way pain is remembered seems to depend on certain factors, including the type of pain or, in other words, its cause, the context, and the meaning it has for the person suffering from it. For instance, episodes of chronic pain, as well as pain related to surgery, are often overestimated at recall. Interestingly, research shows that pain induced by parturition or marathon running is often underestimated at recall despite the fact that both are not only physically grueling but also emotionally intense experiences. However, both processes can likewise be considered positive events, as opposed to most that involve pain. On the neurophysiological level, one of the similarities between giving birth and running a marathon is the particular involvement of the oxytocin system. Oxytocin is involved both in parturition and intense exercise, for various reasons. During labor, oxytocin mediates uterine contractions, while in the case of extensive running it might be involved in the maintenance of fluid balance. It also has well-documented analgesic properties and plays an important role in memory formation and recall. It has been suggested that oxytocin modulates the output of the central nucleus of the amygdala (CeA) during the fear recall. Moreover, it has been demonstrated that oxytocin can impair fear learning and influence the memory of both positive and negative emotionally salient stimuli. We propose that the reason for pain to be remembered in a more favorable light is the central action of oxytocin in the central nucleus of the amygdala, first and foremost during the encoding phase.

Introduction

Pain is defined by the International Association for the Study of Pain as an unpleasant subjective sensory and emotional experience with actual or potential tissue damage, or described in terms of such damage [1]. This experience can be committed to memory and recalled at a later stage. Because of practical implications that the memory of pain has in clinical settings (diagnosis, prevention of serious medical conditions through painful testing) the question of how accurately pain is remembered has been a subject of extensive research [2–6]. The memory of pain has been studied since the early 80s, however, we are still far from reaching a consensus on how accurately pain is remembered [7–10]. Depending on the study, it has been shown that pain memory may be overestimated [4,11–16] underestimated [17–20] as well as remembered accurately [3,6,21–27] at recall. Pain related to surgery is often overestimated [22,28], while dental pain can be remembered accurately [29].

The results of our recent study suggest that the way people remember pain may be dependent on the type and context of the painful experience [22]. Interestingly, most studies on chronic pain indicate that its memory is usually overestimated [2,11,30,31], whereas the memory of labor pain seems to be underestimated [9,32–34]. Moreover, the results of our two recent studies on the memory of pain induced by running a marathon indicate that it is underestimated as well [35,36].

On the psychological level, labor pain and pain induced by running a marathon share an important feature, i.e. they are both associated with a typically happy event of bringing forth a child or a personal accomplishment. Specifically, the meaning that women ascribe to labor pain is a determining factor of their pain experience during labor. When women interpret the pain as productive and purposeful, it is associated with positive cognitions and emotions [37–39]. Thus, both childbirth

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and running a marathon are emotionally positive experiences. In contrast, chronic pain and most other types of acute pain (e.g. surgical, dental) are related to negative events, i.e. illness or a painful medical procedure.

Labor pain and marathon pain share not only positive emotional valence but also some physiological mechanisms. Both parturition and extreme physical exertion involve a number of endogenous systems and substances that are specific to these two types of experiences, including oxytocin [40,41], endocannabinoids [42,43] and endogenous opioids [44,45]. One of them, the oxytocin system, has gained a lot of attention recently in relation to analgesia and memory [46,47].

Hypothesis

We hypothesize that the discrepancy between pain reported during/shortly after the experience and that remembered later in the cases of parturition or intense exercise is caused by oxytocin acting during the event and modifying formation of the memory of its negative aspects. We believe that a higher level of oxytocin released at the time of experiencing pain modulates the encoding phase of memory formation and that it is this phase that differentiates labor pain and strenuous exercise pain from other types of pain. Such a mechanism might reinforce behaviors that lead to experiencing positive emotions which would ensure that the individual would engage in such activity in the future. The interaction of other systems with oxytocin could lead to increased analgesia, but oxytocin would be chiefly responsible for the underestimated pain evident at recall, because of its role in learning and memory, especially when emotionally salient stimuli are involved. We hypothesize that the way oxytocin influences memory of pain is through its activity within the central nucleus of the amygdala (CeA), specifically, its inhibiting action on the CeA during the painful event, i.e. during memory formation.

Evaluation of hypothesis

Oxytocin is a nonapeptide secreted centrally in the hypothalamus of vertebrates. Its action is both peripheral and central. Its best-known peripheral action involves uterine contractions during parturition and lactation in females. In the central nervous system, oxytocin is a neuromodulator involved in social bonding, emotional processing, and pain perception, both on the central and peripheral level, producing an antinociceptive effect [47,48].

The few studies that measured levels of oxytocin after exercise in humans, observed a significant increase in those levels after an ultramarathon but no change if the exercise session was shorter than ~60 min [49,50]. However, some studies indicate such an increase after moderate running or sexual stimulation [51]. Similarly, studies done on animal models demonstrated elevated plasma oxytocin in trained mice [41] and in a study on rats, treadmill training increased oxytocin mRNA expression in paraventricular nuclei (PVN), which is one of the main sources of oxytocin in the brain [52,53]. However, these results seem to be dependent on the type of training, as other studies reported a decrease of oxytocin positive neurons upon resistance training [54]. It seems that there is no obvious physiological reason for the increase in oxytocin. One of the explanations could be the increase in biomarkers of inflammation after strenuous physical exercise. Inflammatory conditions may involve the release of oxytocin [55]. There are quite a few studies suggesting an increase in inflammation in runners after intense exercise [56–58], although a systematic review of such studies showed mixed results [59] mainly due to methodological differences between them. More studies are needed where markers of inflammation and oxytocin would be analyzed in runners who just completed a marathon. Oxytocin was also implicated in the maintenance of fluid balance during strenuous physical exercise [49,54,60], a function typically attributed to arginine vasopressin [49,61].

The role of oxytocin in initiating and regulating parturition and lactation is well known, but its antinociceptive effects in childbirth have not been studied as extensively. In a study by DeBonis and coworkers [62] external oxytocin was less effective as an analgesic than a synthetic analog of oxytocin - carbetocin. The main difference between the substances was the time during which the substance was active, with carbetocin being active 4–10 times longer than oxytocin. A more important role of oxytocin in parturition seems to be triggering inflammation of human uterine tissues and enhancing uterine tone and contractions [40,63]. Oxytocin is also administered to women undergoing a cesarean section in order to prevent postpartum hemorrhaging [64]. Secretion of oxytocin in childbirth is regulated by the opioid system, as evidenced by studies where the opioid antagonist naloxone caused increased release of plasma oxytocin, and the kappa-opioid agonist U50,488 caused the reverse [65,66].

The involvement of oxytocin in social recognition and memory in rodents is also well known [67] and has been reviewed elsewhere [68]. Recent findings from optogenetic manipulation studies show that endogenous oxytocin is crucial for the recognition of previously encountered individuals in both rats and mice of either sex [69–72]. It has also been proven important for the maintenance of social memory [70,73,74]. Oxytocin may be involved in learning and memory in general, as long as emotionally salient stimuli are being used. In a study by Zarei and coworkers [75], intranasally applied oxytocin did not influence the memory of neutral stimuli in macaque monkeys, it did, however, influence the percentage of correct responses when either positive or negative stimuli were used, enhancing the recall of positive, versus negative, stimuli in a delayed matching-to-sample task.

How exactly oxytocin impacts memory formation and recall is not fully understood. Oxytocin fibers have been found in several brain regions involved in memory acquisition, decision making, reward and fear learning such as medial prefrontal cortex, amygdala nuclei, nucleus accumbens and bed nucleus of the stria terminalis [92]. Moreover, oxytocin can protect the hippocampus from the negative effects of stress thus positively affecting spatial memory performance [76,77] as well as stimulate hippocampal neurogenesis [78]. It has been hypothesized that oxytocin can impact on the pain/fear memory on several levels. On one hand it can reduce the activity in brain regions responsible for fear memory formation or retrieval resulting in an acute anxiolytic effect. Such a phenomenon has been shown for example after injecting oxytocin into mPFC and amygdala [68,79]. On the other hand, oxytocin can act via protein synthesis-mediated synaptic plasticity, reflected by long-term potentiation (LTP) or long-term depression (LTD). It has been demonstrated that oxytocin enhances LTP induction in the hippocampus and prefrontal cortex while acting presynaptically to induce LTD in the nucleus accumbens (see reviews for details [68,79,80]).

Some of the results obtained in studies on fear memory acquisition could be potentially explained by the analgesic action of oxytocin, mediated through oxytocin receptor (OXTR). The expression of OXTR has been found in the various brain and peripheral nervous system regions involved in pain perception, such as the spinal cord, the ventral tegmental area, the medial amygdala and the periaqueductal gray matter [81,82]. A small group of parvocellular oxytocin neurons was identified in the paraventricular nucleus of the hypothalamus. Optogenetic manipulation of those neurons resulted in an analgesic effect in an animal model of inflammatory, but not neuropathic, pain [83]. Some studies suggest that the analgesic action of oxytocin is mediated by the vasopressin-1a (V1a) receptor [46,84,85]. Moreover, the direct injection of oxytocin to CeA has an anti-nociceptive effect [86]. However, this effect should not influence recall.

Furthermore, the important role of oxytocin in fear acquisition and extinction in animal models has also been demonstrated [68,87]. It should be noted that most of such data arise from studies using painful stimuli, mostly electric shocks, as unconditioned stimuli [86,89]. Therefore, such manipulations can be interpreted as studies on the memory of pain, although they do not measure it directly. In the fear conditioning paradigm in rodents, oxytocin has a site-specific effect

depending on where and when it is administered within the amygdala nuclei [89]. There it can either increase fear responses or reduce them, when infused to either basolateral amygdala or CeA, respectively. This is particularly important, as amygdala has been shown to be involved not only in processing and memory of fearful events but also reward-based behaviors and encoding valence of stimuli [90,91]. Moreover, a study by Eckstein and coworkers [88] showed that intranasal administration of oxytocin in human subjects led to increased frontal brain activity involved in fear extinction, as well as diminished activity related to fear in the right amygdalar nucleus. Similarly, optogenetic activation of oxytocin release in CeA resulted in fear suppression at recall in fear-conditioned rats [92]. Furthermore, blocking of CeA activity using muscimol or oxytocin agonist injection into CeA had a similar effect [93].

Several studies suggest that oxytocin is involved in disinhibition of the CeA microcircuit implicated in fear responses. This microcircuit consists of two mutually inhibitory cell types within the lateral part of CeA (CeL), one expressing protein kinase C-delta ($PKC\delta^+$) and the other somatostatin (SOM^+) [91,94] The $PKC\delta^+$ mediate a tonic inhibition on the output neurons within the medial part of CeA (CeM), thus suppressing fear behavior. On the other hand, SOM + get activated by the conditioned stimulus, inhibiting, in turn, the PKCδ + cells and thus disinhibiting the CeM output resulting in fear responses. Importantly, many of the PKCδ + cells also express OXTR [94] and were shown to mediate oxytocin-mediated inhibition of the CeM neuronal activity [93,95]. Furthermore, blocking of oxytocin signaling within CeL prevented the suppression of maternal freezing, demonstrating the role of oxytocin in freezing inhibition when the social context was present [96]. Finally, chronic administration of oxytocin results in down-regulation of the OXTR within the CeA [97]. Taken together, it has been theorized that oxytocin modulates CeA output during the fear recall, increasing the CeL PKCδ + cell population activity, thus resulting in diminished fear responses [79]. A similar mechanism might occur during fear learning, as it has been demonstrated that oxytocin microinfusions to CeA impair fear learning [98]. Thus, oxytocin is well suited to modulate not only expression but also acquisition of fearful memories, its role, however, is not limited to modulation of fear conditioning and fear extinction.

To summarize, most evidence supports the claim that oxytocin is involved in learning and memory of emotionally salient stimuli, with most studies done on fear conditioning and extinction. There is a need for more research into the effects of oxytocin in other kinds of memory in order to elucidate the question to what extent the oxytocin is involved in learning and memory in general.

Challenges and consequences of the hypothesis

Our hypothesis is very tentative since the available data is scarce and substantially more research is needed in order to form any conclusion about the subject. Most of the data were collected on rodents since it would be very difficult to assess the central action of oxytocin in humans. Future studies should examine the effect of oxytocin on the memory of pain caused by parturition and intense exercise. Multiple approaches are needed to better understand the influence of oxytocin and its interactions with the other above mentioned systems in forming memories about positive, but painful events. One of the testable consequences of our hypothesis would be increased likelihood of engaging in subsequent satisfying but painful experiences (planning another pregnancy, signing up for another marathon) depending on how much oxytocin was administered to participants.

Another explanation for the underestimation of the recalled pain related to labor or marathon running could be a low level of anxiety during those events (state anxiety). State anxiety is a factor which can influence pain recall [14,15,29]. However, while we have no reason to expect a high level of anxiety about running in marathon runners, a significant number of parturients experience anxiety related to labor [99,100] and it has been shown that cognitive activity in the form of pain catastrophizing during labor can influence the need for pain relief and the obstetric outcome [101–103]. Therefore, since the level of state anxiety may differ between parturients and marathon runners, it does not explain the similarities in the pain recall.

Conclusions

Taken together, both marathon running and childbirth share: 1) the extreme physical challenge, with 2) (usually) positive emotional and social context, 3) confirmed beyond doubt (parturition) or partially confirmed (marathon running) particular involvement of the oxytocin system and 4) underestimated pain at recall. Research shows that both glucocorticoid and noradrenergic activity facilitate the process of strengthening the memory of such experiences [104]. It is therefore surprising to see inaccurate memories being strengthened. Since data on the patterns of release of oxytocin in strenuous physical activity in humans is rather scarce as compared to research exploring its involvement in parturition, and since no direct research has been conducted to date about the influence of centrally released oxytocin on the memory of pain in parturition and marathon running, our hypothesis about the influence of oxytocin on the memory of pain via its central action on the CeA activity is very tentative. More research is needed in order to elucidate what role oxytocin might have in both types of experiences and how well increased release of oxytocin predicts bias in the memory of pain.

Declaration of Competing Interest

The authors declare that they have no competing financial, professional or personal interests that might have influenced the information presented in this manuscript.

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