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MINI-REVIEW

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Oxytocin as Modern Treatment in Some Neuropsychiatric Manifestations. Mini-Review and Original Data

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Abstract

Considering that lately an increased number of authors and reports are suggesting the usage of oxytocin and especially the intranasal oxytocin as a possible treatment or as an additive for most of the neuropsychiatric disorders, and especially those there is an affected social component (e.g. anxiety, depression, autism, schizophrenia, fronto-temporal dementia etc), we will describe here some of the modern research aspects in this area, by focusing on the connections that might exist between the endogenous and/or exogenous oxytocin vs. affective disorders, schizophrenia, autism, cognitive and memory functions, oxidative stress and inflammation, physical exercise, social interrelations, pain sensitivity or neurogenesis related processes, as well as describing some of our original data in this area of research.

Keywords: oxytocin, neuropsychiatry, treatment.

Oxytocin is a neuropeptide hormone secreted mainly by magnocellular neurons in the supraoptic and paraventricular nuclei from the hypothalamus.

The axons of the magnocellular neurons are projected mainly to the posterior pituitary and wrapped up in vesicles, waiting specific neural inputs to release it into the peripheral circulation. Parvocelullar projections include other brain regions such as amygdale or brainstem.

Besides the axonal secretion of oxytocin, there is a specific dendritic secretion that release oxytocin into the extracellular fluid into the hypothalamus [1], where it may have a regulatory function.

In the rat brain, other oxytocin projections have been described in other parts of hypothalamus, thalamus, the amygdala, hippocampus, subiculum, entorhinal cortex, medial and lateral septal nuclei, olfactory bulbs, mesencephalic central gray nucleus, substantia nigra, locus coeruleus, spinal cord, pineal gland and cerebellum [2,3].

The peripheral oxytocin is known to be important in birth, breastfeeding [6] and diuresis [7], but oxytocin may be involved in so many other central processes.

This may be highly speculated when looking at the vast distribution of the oxytocinic receptors [8] and projections in the brain that was already mentioned above.

And most importantly, there is a newly large body of evidence that links oxytocin with several behaviors including social [9], maternal [10] and pair bonding behavior [11], but also with a series of psychiatric disorders including autism spectrum disorder [12,13], anxiety [14], depression [15] and schizophrenia suggesting different possible therapeutic perspectives [16].

Studies reveal that neuropeptides may be mediators in emotion regulations and may be a key element in preserving mood and prevent anxiety.

The strong relations between neuropeptides and monoamines indicated by biochemical studies could explain the importance of oxytocin in the pathogenesis of affective disorders [26].

Even more, the relation oxytocin-depression is further sustained by clinical and animal studies that generally suggest a positive role in depression.

For instance, in postpartum depression, studies found that generally oxytocin concentration is lower comparing to women in postpartum that do not show signs of depression and even a low level of oxytocin during pregnancy may be predictive of depression in postpartum [17,18].

These findings suggest central activity of oxytocin effects postpartum-related, but there are also consistent evidences unrelated to pregnancy, birth and postpartum, that oxytocin system is impaired in depression, but exactly in what way we do not yet know.

While some authors found a decrease in oxytocin level in patients with depression [21], others reported an increase in plasma and salivary levels of oxytocin [22, 23].

Regarding the possible therapeutic functions of oxytocin there are some few reports on humans that suggest antidepressant properties of oxytocin. Scantamburlo and his team found that when resistant depressed patients received additional oxytocin to escitalopram, an improvement in depression symptoms was seen [24].
Several other reports of benefit from oxytocin were indicated by some animal studies on models of depression. For instance, in a series of studies done on animal models of depression, administration of oxytocin improved several behavioral indices suggesting antidepressant effects of oxytocin.

Arletty and his team reported the results of two studies on the effect of intraperitoneal administration of oxytocin in mouse model of depression. In one-time administration study, oxytocin reduces duration of immobility in the behavioral despair test similar to the tryciclic antidepressant imipramine.

Moreover, in a 10-day treatment experiment, oxytocin had even better results than imipramine and significantly diminished the escape failures and the latency to escape in the learned helplessness test [25]. Antidepressant effect of the oxytocin in mice was also consistently demonstrated by Meisenberg [19,20].

Previous data reported benefits of co-administration of oxytocin with the classical drugs used in depression, both in humans as already mentioned, but also in animal models reinforcing the idea of a relation between monoaminergic and neuropeptidergic systems.

In addition, Nowakowska et al. demonstrated antidepressant potency of oxytocin when this was conjunctively administrated with venlafaxine to male Wistar rats.
Moreover, the added oxytocin sustained venlafaxine antidepression functions by maintaining antidepressant activity of venlafaxine, as demonstrated in the forced swim test task [27].

Also, lately there is an increased interest in understanding what could be the exact relationship between central and the peripheral oxytocin [28], with some recent report stating that actually even the peripheral oxytocin could in some condition influence/reach the central oxytocin (e.g. “Oxytocin by intranasal and intravenous routes reaches the cerebrospinal fluid in rhesus macaques: determination using a novel oxytocin assay” in Mol Psychiatry. 2017 or “Increased brain and plasma oxytocin after nasal and peripheral administration in rats and mice” as published in Psychoneuroendocrinology journal) [29-31].

Regarding the connections that might exist between oxytocin and the memory processes, there are reviews in this area of research even from 1979, describing the possible implications of vasopressin and the catecholaminergic neurotransmission in this context [32], as well as contradictory results, since for example 20-25 picograms of oxytocin into the dentate gyrus or the dorsal raphe resulted in reduced passive avoidance (e.g. a the two compartments behavioral task, where in the acquisition trial, each rat is placed in the illuminated compartment and when the animal naturally enters the dark compartment, an inescapable foot shock is delivered; thus the step-through latency in the retention trial is used as an index of retention of the training experience; for example longer retention latencies are interpreted as indicating better retention of the training experience [33]) in rats, while administrating the same quantity of oxytocin in the dorsal septal nucleus generated a facilitation of the aforementioned behaviour in the passive avoidance [32].

Also, complex reviews about this matter are still reported even in the last year, such as the one of Maroun and Wagner, which published in Biological Psychiatry a recent paper relevantly called "Oxytocin and Memory of Emotional Stimuli: Some Dance to Remember, Some Dance to Forget" [34], describing the aforementioned controversies about the so-called cognitive effects of oxytocin. In fact, the authors are proposing an anatomical model to explain the variety of oxytocin effects in this area, by focusing on the differences of some various network sites in the brain, with the main poles being concentrated in the amygdala versus the medial prefrontal cortex [34].

Still, the general studies in this area of research are quite scarce, with some reports stating for example clearly the amnesia-related effects of oxytocin administration on memory in human patients, as a result of a single oxytocin dose administration (e.g. 24 IU), 50 minutes prior some specific tests design to assess both the implicit and explicit memory, such as incidental learning, word stem completion, category-cued semantic association or cued recall [35].

On the other side, Lee et al. [36] demonstrated in 2015 in Nature group paper that intranasal oxytocin administration could actually protect the hippocampal area (well known for its effects in memory – [33] and which is very affected for example in dementia-[37]) from some uncontrollable stress experimental situation which are generating spatial memory deficits, reduced plasticity or decreased long term potentation processes-LTP (e.g. the most important demonstrated model of learning at the cellular level [38]) and increased long term depression (the opposite process to LTP [38]). Moreover, the same authors showed for example that the administration of

a specific oxytocinergic antagonist such as L-368,899 would reverse these facilitating effects of oxytocin, resulting in the aforemetioned hippocampal- related memory and plasticity deficits, as a result of stress [36].

As mentioned, the roles of the hippocampus in the working memory is very important, and besides the classical manifestations when these processes are altered, such as in Alzheimer's disease dementia, there are also reports about how working memory is affected in schizophrenia (e.g. considering the importance of the cognitive functions in schizophrenic patients [39]) and even more important in the present context, how oxytocin could influence working memory manifestation in the schizophrenic pathology [40].

In this way, in the Michalopoulou paper it was showed that one single dose of oxytocin could actually improve the working memory deficits associated with the disorder, as tested in the specific test of Digits Backward score [40].

This could be also connected with the fact that it was quite recently showed that also just one single dose of oxytocin could facilitate higher-order social cognition in schizophrenia [41]. In fact, in the last 2 years there around 17 papers focusing entirely on the matter of oxytocin in the schizophrenic pathology, with controversial and some very different results [42-58], as we already described [in press], suggesting however the increased relevance of this newly proposed therapeutical approach in schizophrenia, but also most of the neuropsychiatric disorders.

Also, our group showed in some small reports in the last few years that oxytocin could facilitate memory manifestations in simple Wistar rats [59], together with some anti-depressive manifestations, as studied in a modified version of the forced-swim test task [60], as well as in other protocols where oxytocin rescued some anxiety, depression and memory deficits associated with a rat model of autism [61], generated through the perinatal administration of the valproic acid [62, 63], some memory deficits in Y maze and anxiety manifestations in elevated plus maze task in a epigenetic rat model of schizophrenia based on methionine administration [64], or with significant ameliorative effects on depression-like manifestations, but no effects on memory in aged Wistar rats at a dose of 10 mg/kg/body weight for 12 consecutive days [65].

Also, when it comes to the relations between oxytocin and aged individuals, we could mention the lasts research grants in this area of study, such as the one performed by the Guastella group in the Brain and Mind Center from the University of Sydney, focusing on "the use of intranasal oxytocin in emotional functioning and reducing career burden in Alzheimer's Disease" [66].

Since we also stated above that there is a connection between oxytocin administration and the autistic pathology, we should mention that there is also an increased awareness directed towards the understanding of intranasal oxytocin relevance in the pathology of autism, with the Guastella group demonstrating for the first time in 2010 that it could actually help only in the context of the easy items vs. hard items in some specific tests (dosage of 18 or 24 IU) [67], while confirming the same results in Molecular Psychiatry in 2016 (24 IU per day for 5 weeks)[68].
However, even in this case there are reports such as the conducted by the Dadds team also in Australia which failed to find any modification as a result of oxytocin intranasal administration (5 days, 12 or 24 IU, depending on weight) on emotion recognition or social interaction skills [69]. Even more, there are papers trying to standardize the mechanical intranasal administration of oxytocin [70], in an effort to reduce the methodological differences between various studies in the literature.
In addition, in relationship to the aforementioned effects of oxytocin it was also suggested that oxytocin administration could actually modulate the neuroendocrine and inflammatory responses, in a close interaction with the so-called oxidative stress manifestations.

In fact, when it comes to the effects exerted by the exogenous oxytocin on the oxidative stress metabolism, the reports are also mixed, with groups demonstrating antioxidant effects on the renal levels [71, 72] or some positive correlations with the reduction of some classical inflammatory markers, such as cytokine production or the nitric oxide [73-75], as well as reducing NADPH-dependent superoxide activity and IL-6 secretion [76], while there are also authors clearly demonstrating some increased oxidative stress status after the administration of oxytocin [77].

Also our group previously demonstrated some antioxidant actions of oxytocin in nude Wistar rats [78], as well as zebrafish behavioral models, where from 2 different dosages that used, only the bigger one resulted in clear antioxidant effects, as demonstrated by reduced levels of SOD and GPX, and increased MDA concentrations [79].

Even more in the aforementioned models of neuropsychiatric disorders [80], we showed some mixed effects of oxytocin administration on oxidative stress status, with no significant modification of the oxidative stress markers which we determined (two antioxidant enzymes: SOD, GPX and a lipid peroxidation marker: MDA) for example in a methionine-induced rat model of schizophrenia, while in aged rats we could see some modifications suggesting a decrease oxidative stress status as a result of oxytocin administration [in press - unpublished results].

In addition, there are reports about that fact some types of physical therapies, including massage for example, could decrease anxiety, by possibly modulating oxytocin release and by decreasing the cortisol levels [as reviewed by [81]). In fact, our group previously described some possible connection between exercise performing (e.g. running on a treadmill) and oxytocin [82], since also other groups described controversial data regarding this interdependence, with reports stating no relation between oxytocin and physical exercise [83, 84] versus modern studies (e.g. two independent studies performed in 2017) where exercising enhanced oxytocin secretion, especially at the cardiac level [85, 86].

Also, these effects could be related to the possible antioxidant actions of some types of exercises (as our group demonstrated for example in performing some bout of bicycle exercise for 40 minutes in untrained subjects [87] or parallel running in adapted treadmills in rats [88], where vitamin C exerted a protective effects against oxidative stress manifestations [87] and possibly smoking [89]), as we also described above in the possible antioxidant effects of oxytocin administration.

There also seems to be a close relationship between the pain manifestations and the endogenous or exogenous oxytocin, since some previous studies suggested a sedative effect for the oxytocin administration (e.g. latency time to increased temperature and mechanical stimuli being increased) [90-94], while there are also undergoing studies focusing on the possible relevance of intranasal oxytocin administration in pain therapeutical management [95], some clearly demonstrated analgesic effects of oxytocin administration (9 minutes of 40 IU: 4 IU of oxytocin every 30 s, alternating between nostrils) after some laser evoked potentials- induced pain of 4 ms [96] and also a related review on this matter in 2014, as presented by the Kerstin Uvnäs-Moberg research group [97].

` Also, it seems that there is a connection between endogenous/exogenous oxytocin versus some gastrointestinal-related manifestations and hormones, as for example Petersson group showed that oxytocin could modulate in time the peripherical concentrations of gastrin, cholecystokinin or insulin (with no effects however on the somatostatin and glucose concentrations) [98]. These effects could be controlled by the vagal nerve [98], although some related HPA axis and cortisol-mediated implications could be perhaps implicated in relation to the oxytocinergic system [97].

`Some other groups (as described in Neuroscience & Biobehavioral Reviews by the Mitchell group [99]) also suggested some analogies between the activation of the oxytocinergic system and the acute alcohol consumption, considering its relative

resemblances on the level socio-cognition, emotions and behaviour. In fact, the aforementioned review, the authors are discussing these resemblances on even bigger scale, finding parallels in a variety of areas between these two systems, such as: fear and stress, trust, social and moral behaviour, risk taking, analgesia, aggression, reward (in relation with oxidative stress? - [100]), trust, altruist or in-group vs. out-group favoritism [99].

Also, in connection with the reward system, oxytocin and animal studies, we could mention here the classical studies involving the vole species (Microtus sp.), where the praire vole are exhibiting a life-long monogamy, while the mountain vole are simply polygamous [101, 102]. Thus, further studies revealed that while there is no difference in the general oxytocin distribution through these two species, there is actually a big difference in how the oxytocin receptors are distributed, with an increased concentration of it in the accumbens nucleus in the praire vole [101, 102], which is an area with a fundamental importance in reward/addition-related manifestations [103]. Even more, blocking oxytocin in the nucleus accumbens of the praire vole will affect the monogameous behaviour of this specie [101, 102].

In fact, in regards with the general implications of oxytocin in the emotional and affective functions, it was previously showed for example in relation to breastfeeding and mood, that the breastfeeding women exhibit increased social interactions levels and reduced depression or anxiety [104], possibly though oxytocin-mediated processes [105], while also others stated that postpartum depression could be related with a decreased breastfeeding duration and also considering the possible connections between anxiety or depression in these cases and oxytocin release during breastfeeding [106].

In the same context, we can mention here the paper of Wudarczyk et al., in 2013, which courageously stated in 2013 about the future possibility that the exogenous oxytocin could actually increase the well-functioning of marital and general type relationships [107], with our group also recently reaching this controversial subject [108].

` In addition, there are reports describing that oxytocin could actually mediate the protective effects after cerebral ischemia for example [109], possible through the aforementioned antioxidant or anti-inflammatory actions described above, effects on microglia or even considering the long-term reductions in blood pressure induced by the administration of oxytocin [110].

Thus, it seems that there are a variety of affective and psychological implications of oxytocin, which can range from the classical types mentioned above

to very different ones, such as those related for example to the modulatory effects of oxytocin in processes such as hypnosis or meditation [111, 112].

Also, mecanistically speaking one of the most important aspects to be mentioned here would be represented by the fact that the exogenous oxytocin mainly administrated though the intranasal route as a very reduced half-life (e.g around to 15 minutes – [113]), suggesting the its effects could be mainly acute, rather than related to a stabile/chronic effect. Of course, this also brings into the discussion the aforementioned secondary mechanisms mediated by the oxytocinergic system. Even more, we should mention here that there are genetic variations in the oxytocin receptors structure [114], which could influence its effects, as well as newly developed knockout mice replicating the oxytocinergic deficits [115].

In addition, some authors described some gender differences in oxytocin modulation [116], with a possible connection for example between the sexual hormones [117] and oxytocin and with reports stating that estrogens can modulate the oxytocin gene promoter [118].

Also, our group is currently working on determining the levels of oxytocin in patients with most of the neuropsychiatric disorders, with some surprising preliminary results suggesting an increase of oxytocin concentration in the peripheral blood of some patients with anxiety, depression, mild cognitive impairment and dementia (Figure 1).

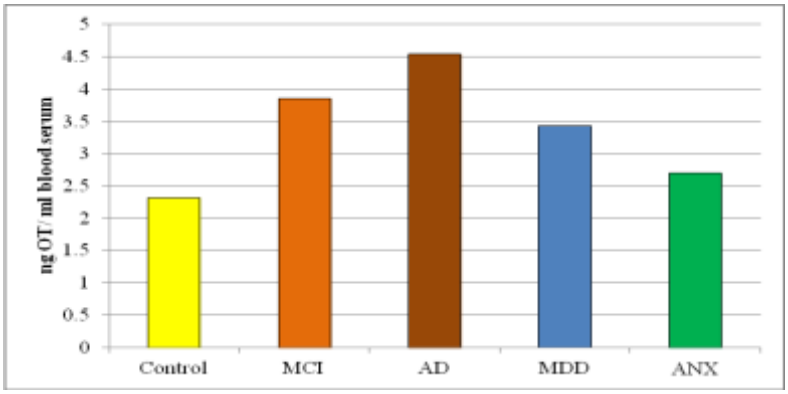

Figure 1. Preliminary results obtained in the serum of patients with mild cognitive impairment (MCI), Alzheimer's disease (AD), major depression disorder (MDD) and anxiety (ANX), as expressed in ng/ml (further statistics, sex differences, treatment influence studies etc are underway).

Another central phenomenon where oxytocin could exert some influence is represented by the hippocampal neurogenesis (which is the process related to the formation of new functional neurons from adult precursors, appearing in some brain regions in mammals, such as the hippocampus, the lateral ventricle or the olfactory bulb – [119]**)**, that could be sufficient for example in decreasing depressive and anxiety-like behaviours, as for example the 2015 study performed by Hill et al clearly demonstrated [120]. Even more, there are direct studies showing that oxytocin is increasing neurogenesis even under stressful conditions [121], with some authors suggesting oxytocin future usage as full antidepressant, based on these neurogenesis-stimulating effects [122].

` Thus, in conclusion we can say that oxytocin is a complex neuropeptide that must be understood in relation to a certain biological and social context and it would be restricting to describe as having a specific positive or negative role may not be accurate. The notion of a positive role of oxytocin in social behavior including emotional regulation, tends to be outdated since numerous evidences favor also for a negative role such as aggression or fear. In this context, having opposite effects and being reactive to so many factors, oxytocin may be conceived as a regulating neuropeptide contributing together with many other systems in adapting the organism to the changing conditions while preserving the integrity and the stability of the organism. However, the functions of oxytocin and its effects in most of the neuropsychiatric disorders are warranting future studies in this area of research.

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