

Can Oxytocin function as an antidepressant?

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Introduction

There is much criticism on the efficacy of anti-depressant drugs currently available. Most anti-depressant drugs have been serendipitous discoveries and the mechanism underlying their anti-depressants working are poorly understood.¹ The currently available anti-depressant work to some degree, but are far from ideal. Psychological studies have revealed that many of the new drugs (SSRI's, NRI's, SNRI's) may have a placebo affect of 70-80%. A more structured approach to finding a good anti-depressant seems needed, instead of again hoping on good fortune to bring us an improvement.

In recent years the physiological processes that are involved in causing depression, have been studied extensively. There are many studies that have pointed toward an intricate involvement of the hypothalamic-pituitary adrenal (HPA) axis in depression and depressed behavior.³ A hyperactivity of HPA seems to be a clear physiological indicator of depression. Furthermore, the current anti-depressants may also have an effect on the HPA activity. Most antidepressants (SSRI's, NRI's, SNRI's) have the same clinical profile even though they have an effect on different systems. They all require between 2 to 6 weeks before they take effect and suppress depression. The long time between administration of the drug and its effect, causes one to believe that it is adaptation to the drug administration that has is reducing depression, rather than the drug itself. Holsboer filled this gap by suggesting that the anti-depressant action of reuptake inhibitors work on the HPA axis, rather than on the targeted system. The constant binding of receptors in the post-synaptic nerve cell cause the transcription factor CREB to be less phosphorylated and active, which in turn inhibits the translation of a HPA hormone corticotrophin-releasing hormone (CRH). CRH is the primary upstream hormone in the HPA. This would then lead to the normalization of the HPA hyperactivity observed in depression. This process is shown in a scheme (figure 1).

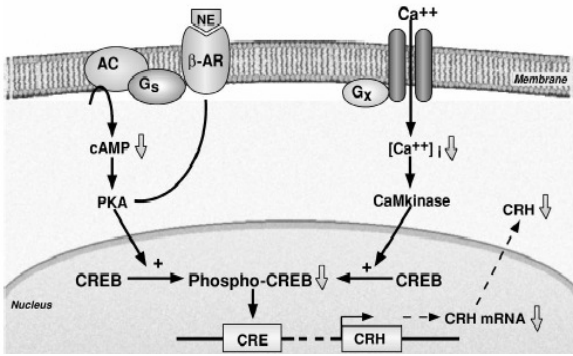


Figure 1 Postulated effects of antidepressants leading to decreased activation (phosphorylation) of abundant cAMP-response element-binding protein (CREB) and subsequent decrease of CRH gene expression.²

The involvement of the HPA in depression leads one to suspect that rather than interrupting secondary systems, antidepressants may work on the HPA axis through a downstream mechanism.² However; none of the current antidepressant drugs work directly on the HPA axis and are in fact chance discoveries. Uncovering the mechanisms through which HPA is involved in the pathology of depression and finding drugs that suppress these mechanisms opens a door to a whole new treatment of

depression. Whether HPA axis overdrive is the cause or an effect of depression remains unclear and it's a bit of a chicken and the egg discussion.⁴ Neither the less depressed patient display an array of pathological behaviors that are indirectly correlated to a hyperactive HPA axis. They display a lack of concentration and memory, high irritability, which are signs of high stress. Also they show social behavioral patterns less associated to HPA axis activity, such as decreasing social interest and a tendency towards social isolation, which might be a secondary effect of HPA axis activity in combination with other regulators of social behavior. Here oxytocin comes into play, because it's a regulator of both HPA axis and social behavior. Oxytocin might provide a link between pathological behavior seen in depression and the HPA axis hyperactivity, as well as introduce a new target for antidepressant therapy. Oxytocin is a neuropeptide and hormone that is produced by the hypothalamus. Recently oxytocin has caught the eye of many scientists as a potent modulator of behavior, especially of social behavior. Oxytocin also has a profound effect on trust/bonding behavior,^{5, 6} anxiety-related behavior⁷⁻⁹ and social recognition.¹⁰⁻¹² Oxytocin is also a modulator of HPA axis activity. It has been shown that oxytocin in the brain and the blood suppresses HPA activity.^{9, 13} Through these mechanisms oxytocin has been implicated to have an effect on many different psychiatric disorders including depression.¹⁴

All these facts point toward oxytocin as being a good target for decreasing the HPA hyperactivity, anti-social behavior and anxiety in depressed patients. Oxytocin might be a potent modulator for various behavioral symptoms of depression and oxytocin deficiencies might play a role in the pathology of depression. Therefore this paper will assess the potential of oxytocin to function as antidepressant?

The role of HPA axis in depression

The connection of depression and the HPA axis needs to be clear and well understood, before one could target it as a system that modulates depression. In depressed patients high levels of glucocorticoids, mainly cortisol, have often been reported.² Cortisol is one of the main hormones involved in a responses to stress. Glucocorticoids increase protein breakdown and conversion into glucose, help make fat available for energy, increase blood flow and stimulate behavioral responsiveness in response to stress. These are all processes quite vital to an adequate response to stress and even for life all together.¹⁵ The hypothalamic-pituitary adrenal (HPA) axis has been identified as a key player in release of cortisol. The HPA axis starts the regulation of cortisol secretion in the paraventricular nucleus (PVN) of the hypothalamus. These neurons secrete a peptide called corticotrophin-releasing hormone (CRH). CRH reaches the pituitary gland where it stimulates the secretion of adenocorticotrophic hormone (ACTH), which enters the bloodstream. At the adrenal cortex ACTH stimulates the release of glucocorticoids into the blood.¹⁵

Depression coincides with HPA hyperactivity

The HPA axis is a key component in the stress response. A hyperactivity of HPA axis can be pathological and is closely linked with depression.^{2, 3}

COURSE OF DEPRESSION PREDICTED BY HPA ASSESSMENT

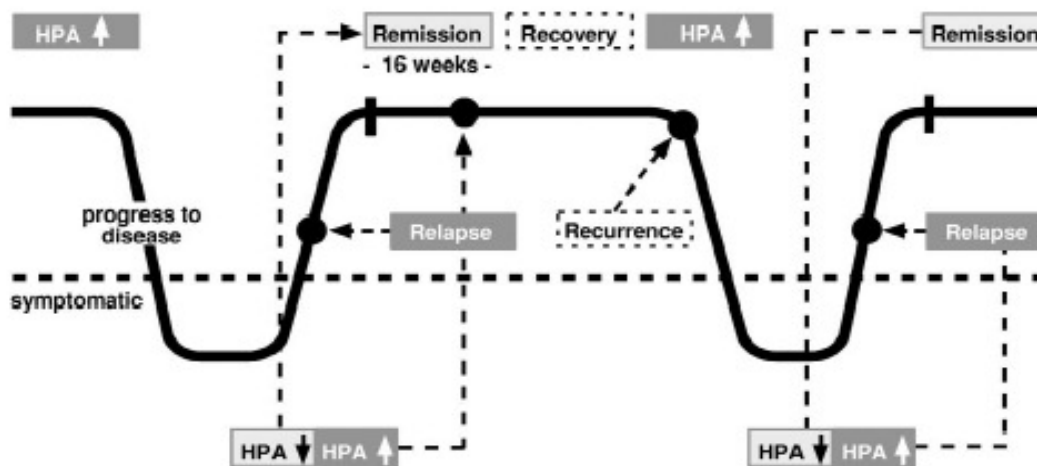


Figure 2 Postulated relationship between the course of depression and HPA system regulation.²

Figure 2 shows a scheme that according to Holsboer represents the HPA and its correlation in depression. In relapse periods HPA activity is elevated, indicating it coincides with a depressed state. When the depression subsides HPA activity normalizes. HPA activity is already used as a tool in measuring depressions and relapse chances. The DEX/CRH test has proven to be a very solid indicator for relapse chances after anti-depressant treatment. In the DEX/CRH, depressed patients are pretreated with glucocorticoid receptor antagonist dexamethasone and given a CRH injection. Depressed patients have an elevated cortisol and ACTH response to the CRH injection.² This indicates that the dexamethasone pretreatment is less capable to suppress the HPA response to the CRH injection in depressed patients and that their HPA response to stress is elevated.

That depression and HPA axis hyperactivity correlate is quite clear. However it is still unclear how this correlation translates into the cause and effects of depression. HPA hyperactivity might well be an effect of depression and suppression of the hyperactivity might not directly alleviate depression. After all administration of cortisol or corticosterone do not induce depressive behavior. What is more likely is that there is an interaction between being depressed and the HPA axis. To make an effective anti-depressant it is important to know the mechanisms of this HPA hyperactivity and what its contribution is to depression. This is where the behavioral aspects come into play. This will be discussed that later in chapter 3.

The hyperactivity could be situated at different levels in the HPA axis. At the adrenal level glucocorticoids receptor expression and sensitivity could increase cortisol secretion. At the pituitary gland hormones in the blood could modulate ACTH release. In central nervous system(CNS) the secretion of CRH could be excessive, detected by to CRH receptor insensitivity, leading to hyper secretion of ACTH.^{2, 16} At this moment hyper secretion of CRH has the most prospects to be involved in depression, because it is the most upstream regulator of the stress response and is involved in the anxiety related physiology.

CRH hyper secretion

CRH has a lot of different effects on the physiology of mammals. In figure 3 there is a global scheme of the different signs and symptoms correlating with depression and the secretion of CRH.

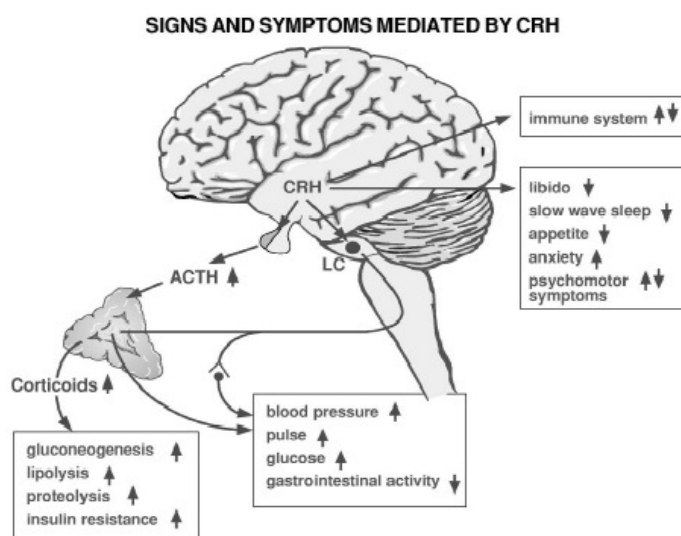


Figure 3 Animal studies in which CRH was injected intracerebroventricularly or in which CRH synthesis was disrupted (knockout mice or antisense oligodeoxynucleotide treatment of rats) or CRH receptor function manipulated through antagonists, gene therapy or gene targeting are in accord with indirect clinical evidence that many signs and symptoms present in depression can be attributed to enhanced secretory activity of central CRH.²

Many studies indicate that HPA hyperactivity in depression clearly correlates with elevated CRH level through hyper secretion of CRH in the brain. Depressed patients have elevated CRH levels in the cerebral fluid. Also suicide victims who suffered from depression had diminished CRH binding and increased numbers of CRH secreting neurons. Depression clearly correlated with increased CRH activity in these people. Early life events associated with the development of depression, may cause long-term alterations in the CRH neurons which may increase vulnerability to binding and anxiety disorders. Social isolation with primate causes hypercortisolism, caused by long-standing CRH neuronal hyperactivity.³ Maternally deprived rats show increased expression of CRH mRNA in the PVN and increased CRH secretion. These life events enlarge the chance of the onset of depression³ and this may be mediated by the increased CRH secretion. Also, as expected, successful treatment of depression normalizes the CRH hyperdrive.² This is all strong evidence that hypersecretion of CRH in depressed patient is the driving force behind the HPA hyperactivity in depression.

Whether the CRH hyperdrive is a cause or a result of the HPA hyperactivity remains to be seen. Considering that CRH is one of the more upstream neuropeptides in the HPA axis suggests that it is rather the cause than a result, but negative or positive feedback could also have a direct influence on the CRH secretion. In Table 1 there is a summary of the evidence that central CRH hyperactivity is linked to depression and a depressed state.

Table 1 Evidence suggesting hyperactivity of central CRF systems in depression³

- Elevated CSF CRH concentration in drug-free depressed patients
- Normalization of elevated CSF CRH concentration with successful anti-depressant treatment
- Decreased CRH receptor binding sites in the prefrontal cortex of suicide patients
- Hyperactivity of HPA axis in depressed patients
- Elevated CRH concentrations and CRH mRNA in hypothalamic PVN of depressed patients
- Elevated CSF CRH concentration in adult primates previously exposed to early-life stress, which is associated with an increased risk for depression in humans
- Elevated concentrations of hypothalamic and extra hypothalamic CRH in adult rats previously exposed to early-life stress

It is clear that CRH hyperdrive might be a target for anti-depressant treatment. CRH receptor antagonist could be a good target for new anti-depressants.² Even antagonists of CRH in general can be candidate for anti-depressant treatment. If the CRH hyperdrive can be normalized this might increase effectiveness of other anti-depressants and it might be useful as an anti-depressant on its own. There still remains the question if this centrally elevated CRH level strictly influences the HPA axis. Elevated mRNA in the PVN is a good indicator that there is interaction with HPA activity. But CRH levels might influence many more parts of the brain and again there is a cause and effect game to be played. Is the elevated CRH in the brain a cause or an effect of depression, or both? Recently there has been a fierce discussion whether or not HPA axis hyperactivity and CRH hyperdrive, which is potentiated by oxytocin sister neuropeptide vasopressin, is cause or effect of depression.⁴

This is where oxytocin adds a new dimension to this discussion. If oxytocin can attenuate the HPA axis properly and not only decrease CRH hyperdrive but also the somatic symptoms of depression it might provide a link to associate HPA-hyperactivity to the behavioral aspects of depression. An indication for oxytocin potential is the fact that oxytocin can regulate the HPA axis upstream in the brain, before the synthesis of CRH.

Oxytocin and its effect on the HPA-axis regulated stress-response

Considering the clear correlation of depression and HPA hyperactivity, the effects of oxytocin on the HPA axis need further attention. If oxytocin can suppress HPA hyperactivity in combination with positive behavioral effects it can link HPA to depressed behavior and provide a broader range of effect on depression than current anti-depressants. The influence of oxytocin (OXT) on different levels of the HPA-axis activity was the focus of much research. It seems to play a role in modulating the release of corticotropin releasing factor (CRF) and glucocorticosteroids. Oxytocin is a neuropeptide/hormone that is produced by Hypothalamic-Neurohypophysal System (HNS). The HNS consist of the magnocellular neurons of the paraventricular nucleus (PVN) and the supraoptic nucleus (SON). The SON and PVN synthesis arginin vasopressin (AVP) and OXT. Projection to the postior pituitary gland causes secretion of OXT and AVP in the blood circulation. The HNS also releases OT and AVP into the extracellulair fluid of the PVN and SON. There it can influence other areas of the brain as well as the PVN and SON itself. The extracellulair release of OXT and AVP does not necessarily coincide with secretion of OXT and AVP into the blood. (Engelmann 2004)

There are two basic functions of OXT. One is its function as neuropeptide or modulator in the central nervous system (CNS). Secondly, it has a function in the periphery as a hormone. First we'll discuss the effect of OXT acting as a neuropeptide.

Oxytocin as a neuropeptide

Neumann suggested that the influence of OXT in the brain on the HPA- axis works according to this scheme:

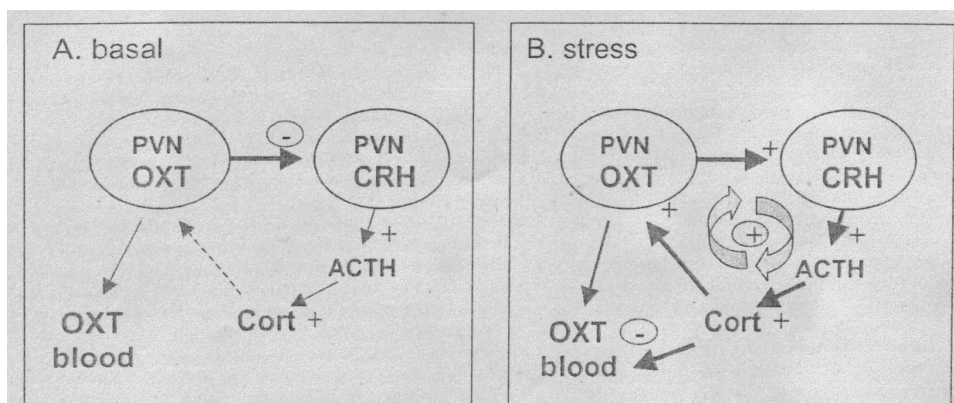


Figure 4 Hypothetical scheme demonstrating interactions between OXT and the HPA axis at the level of the hypothalamic PVN under basal (A) and Stress (B) conditions. -, inhibitory effect, +, excitatory effect; dashed line; no effect.¹⁷

This scheme suggests that OXT has an inhibitory effect on the HPA at basal level but an excitatory effect when stressed. Neumann found that retrodialysis of OXT antagonist into the PVN decreased HPA activity after a forced swim experiment, indicating an excitatory effect of OXT in PVN on the HPA axis during stress (Fig. 4). Neumann also found that in resting condition microdialysis of OXT antagonist in the PVN increased HPA activity. This indicates that OXT causes a tonic inhibition of the HPA axis in resting conditions.¹⁷ Research by Neumann concluded also that oxytocin antagonist introduced in the lateral cerebral ventricle decreased basal release of

ACTH and corticosterone. This indicates that oxytocin increases the activity of the HPA-axis in stressed condition.

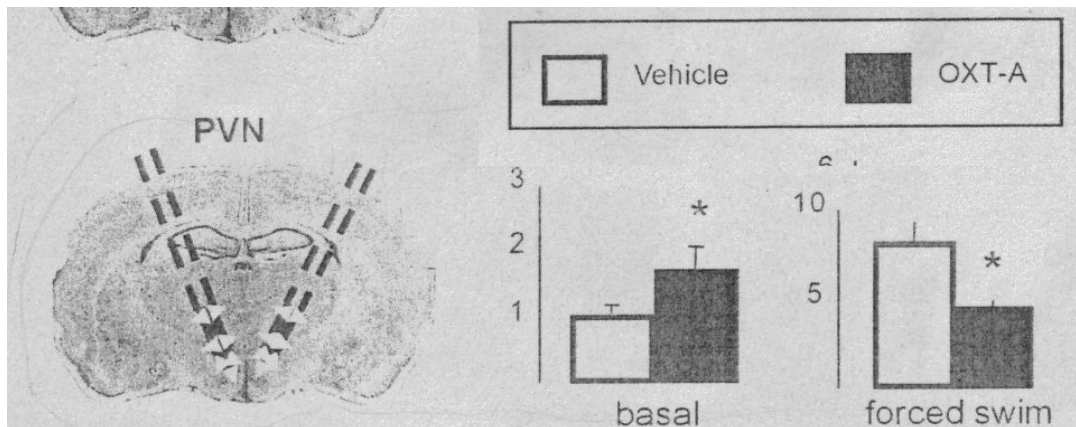


Figure 5 Effects of local administration of the OXT receptor antagonist (OXT-A) into the PVN via retrodialysis on basal and stress-induced ACTH secretion of male Wistar rats. Presented are the ratios of ACTH plasma concentrations after and before OXT-A under basal conditions (basal) and after and before stress-exposure. Data are the mean \pm SEM $P < 0.05$ versus vehicle.

Other studies have found an inhibitory effect of central oxytocin on HPA axis activity when stressed.^{9, 13, 18} These experiments provide evidence for an attenuating effect of brain OXT. Figure 6 shows the result of an experiment with rats in response to noise stress. The levels of corticosterone were measured and oxytocin was pumped into the 3rd ventricle in different doses. In figure 6 the corticosterone level of the rats in response to noise stress is significantly lower when 10ng/h or 100ng/h of oxytocin is administered. This reduction worked in a dose dependent manner.

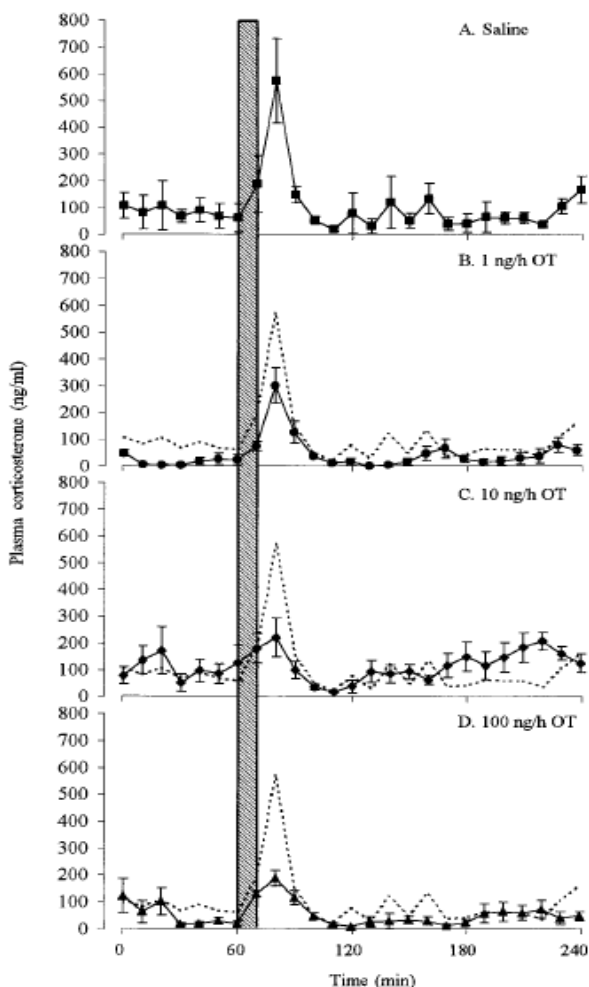


Figure 6 The effects of white noise stress (114 dB for 10 min; hatched bar) on plasma corticosterone concentrations of ovariectomized, estradiol-treated female rats infused centrally with isotonic saline at a rate of 0.52 ml/h (A; n 5 6) or supplemented with oxytocin at a rate of 0.1 ng/h (B; n 5 5), 10 ng/h (C; n 5 6), or 100 ng/h (D; n 5 6). Each point represents mean \pm SEM for the given group sizes. For comparison, the control values are shown in B–D by the broken line. ANOVA revealed a significantly smaller response to the stress in animals treated with either 10 or 100 ng/h oxytocin compared to that in the saline-infused controls ($P < 0.05$).¹⁸

The reduction in anxiety and corticosterone indicates a moderating effect of OXT on stress physiology. OXT deficient female mice displayed more anxiety and had elevated corticosterone level when exposed to a psychological stressor. But baseline corticosterone and anxiety level were not elevated.⁸ OXT appears to have an effect on stress-response and coping but not on baseline levels of the HPA activity. This is the complete opposite of what Neumann's scheme suggests.

Research with intranasal administration has been performed more recently. Especially after evidence that intranasal administered neuropeptide reached the brain was provided.¹⁹ This opened the door to administration to primates and humans. In monkeys intranasal administration of OXT attenuates the ACTH response to acute social isolation, but it had no significant effect on cortisol levels. The absence of an effect of cortisol levels may have been due to a short assessment period in which the cortisol level had not yet responded.¹³ The reduction in ACTH indicate a reduced activity of the HPA-axis.

In humans, the effect of intranasal OXT administration was tested with a TSST-test. The TSST-test is a psychosocial stress test involving a presentation in front of a group and an

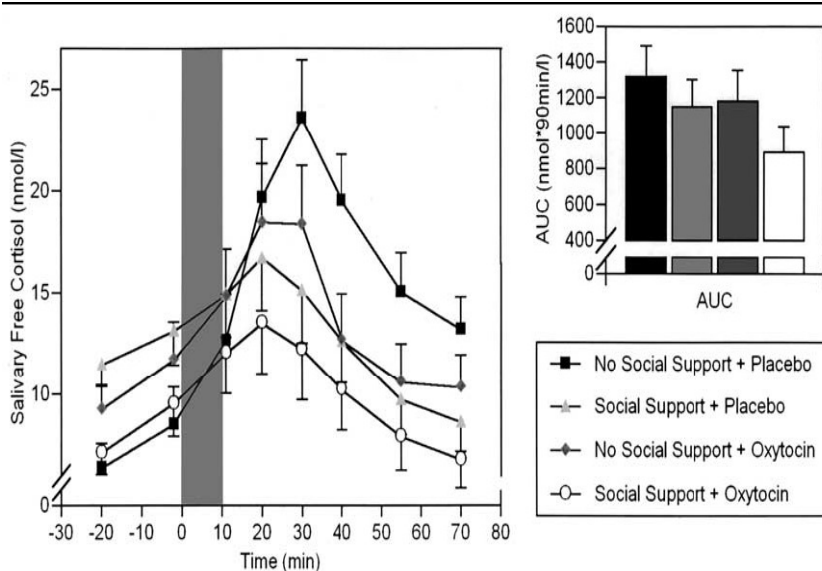


Figure 8 Mean salivary free cortisol concentrations (\pm SEM) during psychosocial stress exposure (Trier Social Stress Test). Participants were randomly assigned to receive intranasal oxytocin (24 IU) or placebo and either no social support or social support from their best friend before stress. The shaded area indicates the period of a public speaking task followed by mental arithmetic in front of a panel of evaluators. The areas under the individual response curves aggregate the eight saliva hormone levels during the stress protocol. Significant interaction effect on cortisol

was obtained (social support x time effect, $p < .001$; social support x oxytocin x time effect, $p < .01$).⁹

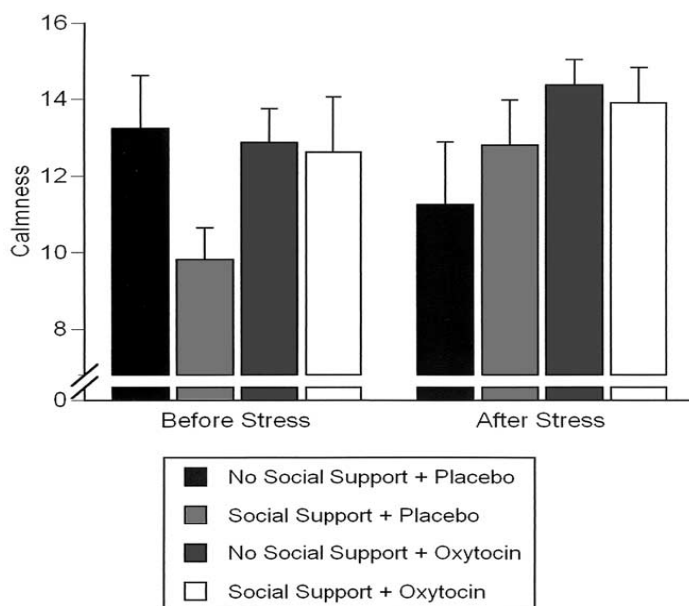


Figure 9 Mean (with SEM bars) levels of calmness as a function of study group and time of measurement (before and after stress). Significant three-way interaction effect on calmness was obtained (social support \times oxytocin \times time effect, $p = .05$).⁹

arithmetic test. Calmness before and after the test was also measured. The results of this research are shown in fig.8 and fig. 9. Figure 8 show the cortisol levels of the different groups, measured in their saliva. In figure 8 one can see that social support greatly decrease cortisol level in the test subjects. Oxytocin seems to increase the effect of social support on the cortisol levels, causing them to decrease even further. They also tested the calmness of the study group (fig. 9). In figure 9 the calmness of the oxytocin only group is greater after stress than the control. This comparison of calmness reveals that OXT has an anxiolytic effect. Also OXT enhances the reduction in anxiety and cortisol levels due to social support.⁹ OXT doesn't alter the stress response directly at an adrenal level put prior to adrenal activation.¹³ These are another indication for an inhibiting effect of OXT on the HPA-axis endogenously. In summary central OXT administration seems to have a varied effect on the HPA axis activity, very much dependent upon the place of administration. When OXT its introduced more generally its seems to inhibit the HPA axis, both at stressed^{9, 13, 18} and basal levels.¹⁷ When it is introduced specifically into the PVN OXT has a excitatory effect on the HPA in combination with a stressor.¹⁷ This suggests that OXT has an effect on a broad range of areas in the brain, as the presence of OXT receptors in many parts of the brain suggest.^{20, 21} OXT might inhibit the HPA through other parts of the brain. Retrodialysis of OXT antagonist in the amygdala and the septum show a minor increased activity of the HPA.¹⁷ This may point to and cumulative effect of small inhibition or modulation of OXT through several parts of the brain, leading to a larger inhibition of the HPA axis. Oxytocin attenuating effect on the HPA axis found in these animal models has been confirmed in other models.²²

Oxytocin as a hormone

In peripheral experiments, OXT was usually injected in the bloodstream. In rats 30 minutes after OXT injection corticosteron and ACTH levels were raised. After 2 hours the corticosteron and ACTH levels had normalized. After 6 hours corticosteron levels were lower that controls, but ATCH level remained equal.²³ A 5 day treatment of OXT reduced corticosteron level but not ACTH level for a period of 10 days. OXT pretreatment seems to sensitize the inhibitory feedback systems for corticosteron.²³ All this points toward an inhibition at the adrenal level.

Infusion of OXT in normal male humans induced a decrease in plasma cortisol levels, that was dose dependent.²⁴ It also decreased ACTH levels suggesting action at the hypothalamic-hypophysal level.²⁵

In general OXT in the blood decreases glucocorticoid and ACTH levels, both at adrenal and hypophysal level. The effect of peripheral OXT on behavior has not received a lot of attention, but considering that OXT can't pass the blood-brain barrier this might not be interesting. OXT in the blood does have a direct inhibiting effect on the HPA axis.

In humans lowered oxytocin has been associated with increased HPA activity. An experiment with schizophrenic patients showed a drastic increase in glucosteriods coincides with a decrease in plasma oxytocin levels in response to a stressor.²⁶

Summary

In the periphery OXT clearly decreases HPA activity, through inhibition either at the hypophysal or adrenal level.²³⁻²⁵ Whether this mechanism sensitizes inhibitory feedback for corticosteron²³ or decreases the ATCH secretion²⁵ remains to be seen. It is clear that OXT has a pronounced effect on the HPA axis in CNS. Centrally OXT seems to have a complex interaction with several parts of the brain. OXT can both inhibit and excite the HPA axis depending on which region of the brain OXT interact with. It is not clear yet how these mechanisms influence each other. OXT in the PVN seem to be excitatory combined stress while inhibiting at basal levels. In other regions OXT has been reported to inhibit HPA activity.¹⁷ While general administration in the brain has shown an inhibition of the HPA as well as an anxiolytic effect. OXT must exert its inhibition on the HPA through several different regions of the brain.^{9, 13, 18} This mechanism may have a sensitizing effect on inhibition of CRH secretion, but it could also have a direct effect on CRH secretion. It deserves investigation to find out in which parts of the brain OXT exerts inhibiting, thus excitatory action on the HPA. Then a clear map can be made of the way OXT influences the secretion of CRH and the activity of the HPA axis. This may also offer an explanation for the effect of oxytocin on behavior and anxiety in combination with a decrease in HPA activity. Therefore we will venture a little deeper into oxytocin effect on behavior and its effect on different part of the brain.

Oxytocin's effect on behavior

As state before oxytocin is a potent modulator of behavior. It facilitates trusting and bonding behavior in many different species, including humans.^{5,9,27} Oxytocin is also involved in social recognition²⁸⁻³⁰ The question remains if this effect of oxytocin on behaviour is related to its effect on the HPA-axis. There is a clear correlation between stress and behaviour; oxytocin might tap in to this correlation to either exert its effect on the HPA-axis to influence behaviour or vice versa. More likely is that it is not as straight forward and the relation between these effects is a mix of cause and effect. We will venture into this effect of oxytocin on behaviour and its relationship to the HPA-axis.

Oxytocin's effect on anxiety

Oxytocin and its receptors have been tested in a wide variety of stress-coping paradigms. In rats oxytocin showed an anxiolytic effect when administered centrally. Windle used the plus maze paradigm to test anxiety in rats. They found that placing rats in an unfamiliar testing facility effect exploration behaviour and made rats more anxious. In both a familiar and unfamiliar setting rats were injected with oxytocin (Figure 10). Rats continuously infused with oxytocin were more explorative and therefore less anxious in this paradigm when compared with controls.⁷ This indicates that central oxytocin administration in the brain has an anxiolytic effect. Research was also done to investigate the endogenous effects of oxytocin on different parts of the brain. The studies looked mostly at the anxiety related effect of oxytocin on the amygdale, medial prefrontal cortex and hypothalamus. In the hypothalamus and medial prefrontal cortex infusion also had an anxiolytic effect.³¹ Knock-out mice show reduced anxiety related behaviour only in pregnant female rats.¹⁷ Indicating that being in a peripartum is a prerequisite for the anxiolytic effect of oxytocin. However over expression of oxytocin receptors in the amygdala in virgin female rats also increased anxiety levels.¹⁴ This stipulates the fact that effect of oxytocin administration varies greatly depending on the place of administration in the brain.

Oxytocin, HPA-axis and ERK1/2

We can conclude that oxytocin decreases anxiety related behaviour in concordance with decreasing HPA-axis activity. This indicates a relationship between HPA-axis activity the anxiolytic effect of oxytocin. HPA-axis activity has been related to

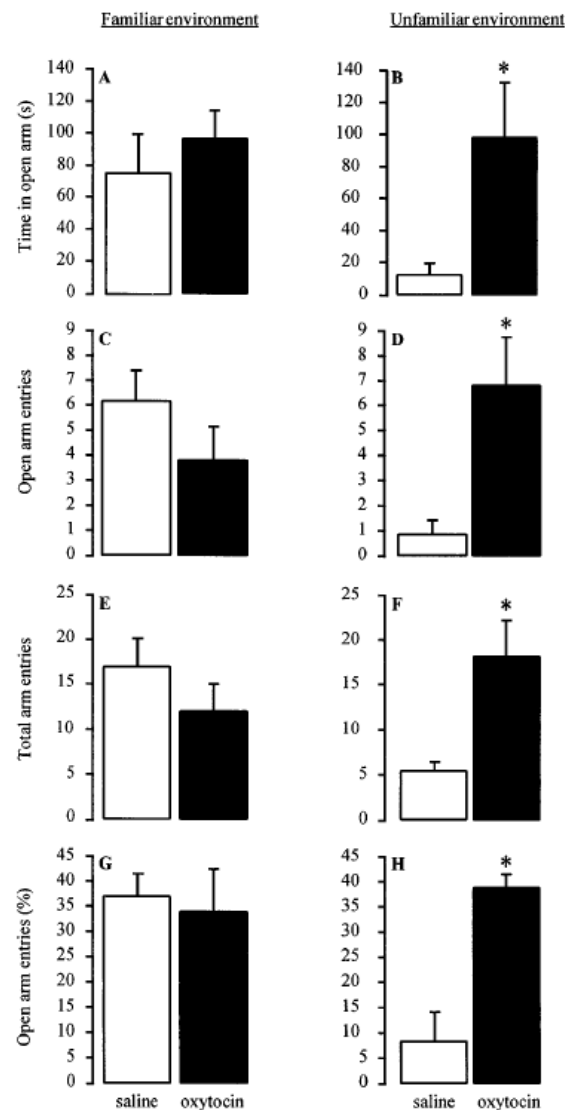


Figure 10| The performance of ovariectomized, estradiol-treated rats during a 15-min period on the elevated plus-maze. *Open bars* represent animals infused centrally with isotonic saline alone (0.52 ml/h), and *closed bars* represent infusion of oxytocin at 100 ng/h. *Left panels* (A, C, E, and G) represent measurements from animals that were housed and tested in the same environment. *Right panels* (B, D, F, and H) represent measurements from animals that were tested in an unfamiliar environment. The parameters shown are time spent in the open arm (A and B), open arm entries (C and D), total arm entries (E and F), and open arm entries as a percentage of total arm entries (G and H). All values represent the mean \pm SE for groups of six animals. *, P , 0.05, by Student's t test compared to saline-infused controls.¹⁸

increased anxiety. Jaferi et al. found that CRH injection in medial prefrontal cortex increased anxiety related behaviour. This was tested in the open-arm-plus-maze paradigm with acutely and repeatedly restrained rats.³² CRH also had anxiogenic effects when administered in the amygdala.³³ So the likely between oxytocin and its effect on anxiety might well involve CRH or a related mechanism, one of these related mechanisms is the extracellular signal-regulated kinase (ERK) 1/2 cascade. Oxytocin can activate ERK1/2 (MAP kinase) cascades³⁴; these pathways can also be activated by CRH in different regions in the brain.³⁵ In two paradigms, the lightbox and open-armed-plus-maze, Blume et al. found that oxytocin infused in the PVN had an anxiolytic effect. This anxiolytic effect was specific for the PVN and could be undone by blocking the ERK MAP kinase cascade with MEK inhibitor U0216, see figure 12.³¹ This indicates that the anxiolytic effect of oxytocin in the PVN works through activation of ERK1/2, suggesting that these cascades are causally involved in Oxytocin's anxiolytic effect. Recently it was also shown ERK1/2 inhibition in the dorsal hippocampus and medial prefrontal cortex induced depressive like behaviour in rats. This was also tested in anxiety related paradigms for depressive behavior. In the elevated plus maze the rats spend less time on the open arms (figure 11), indicating anxious behavior. The same induced anxiety was seen in the open field test. The reduction in anxiety correlated with a reduction in phosphorylation of cyclic AMP-responsive-element binding protein (CREB) in the medial prefrontal cortex.³⁶ This is a link back to what Holsboer proposed as the effector pathway in current SSRI treatment.² It is likely that oxytocin can induce this CREB phosphorylation through ERK1/2 activation. CRH mediated ERK1/2 inhibition was also found to decrease depressive like behavior. In this study they used CRH receptor deficient mice, which displayed more depressive like behaviour in the forced swim test and tail extension test.³⁷ These recent studies provide a bit of a controversy. In the same paradigms as Todorovic. Qi et al. also found that stressed rats had decreased ERK1/2 and CREB activation and that fluoxetine (an SSRI) restored ERK1/2 activation as well as alleviate depressed behavior. This reinforces the speculation that ERK1/2 might be

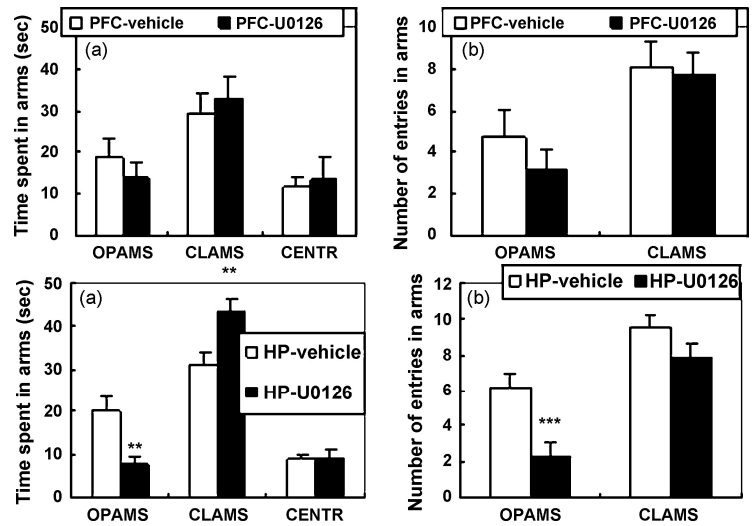


Figure 11 The effect of the inhibition of ERK pathway in HP (dorsal hippocampus injection) and PFC (medial prefrontal cortex injection) on the time spent in arms (a) and the number of entries into arms (b) in elevated plus maze in rats. OPAMS, open arms; CLAMS, closed arms; CENTR, central area. Data expressed as mean \pm S.E.M., $N = 10-12$ per group. ** $P < 0.01$ and *** $P < 0.001$ ³⁶

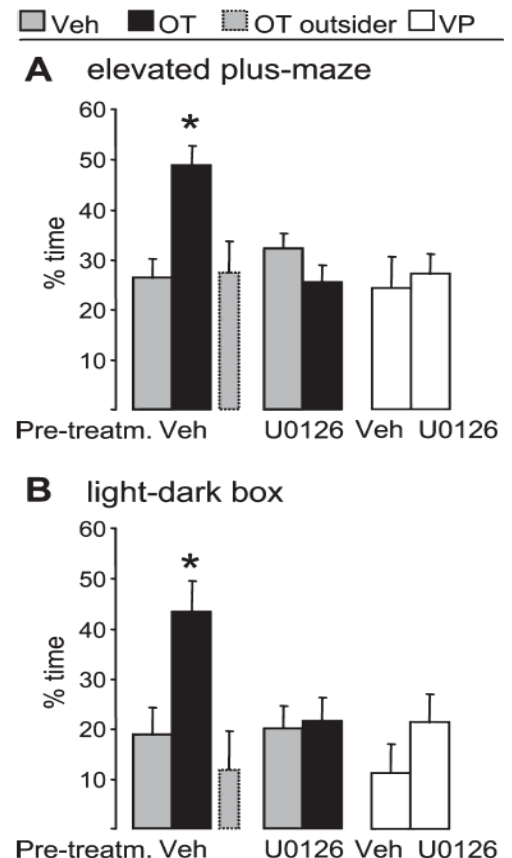


Figure 12 Inhibition of the anxiolytic effect of oxytocin (OT) within the PVN by local pretreatment with the MEK1/2 inhibitor U0126. (A) Percentage of time spent on the open arms as an indication of anxiety-related behaviour on the elevated plus-maze, and (B) the percentage of time spent in the lit. compartment in the light-dark box. Rats were pretreated with bilateral microinfusions into the PVN of either vehicle (Veh) or U0126 0.5 nmol/0.5 μ L, followed by either Veh, OT (0.01 nmol/0.5 μ L) or vasopressin (VP; 0.01 nmol/0.5 μ L). Behavioural data of animals with the injection site outside the PVN are indicated. Data represent means \pm SEM; * $P < 0.05$ vs all other groups³¹

potentially targeted as antidepressant.³⁸ These studies reveal a complex network of feedback loops, in which it is still unclear under which circumstances ERK induces or reduces CRH production.

Oxytocin's effect on social behavior HPA mediated?

The connection between oxytocin, HPA-axis, ERK1/2 opens up an interesting connection for oxytocin to effect anxiety and depression. The question remains if modulation of the HPA-axis also affects more secondary social and behavioural dysfunctions as social isolation and disregard, high irritability, lack of concentration and memory. Possibly these phenomenon are related to anxiety related behaviour and HPA-axis activity.

The relationship between HPA-axis and social behavior is not very clear. There have been a few psychological researches that address this subject, but the cellular and physiological background is not clear at all. It was found that high cortisol levels corresponded with a decreased ability for social recognition in response to social stress.³⁹ There are a few more hints toward this direction. In monkeys, a relationship was found between social rank and HPA-axis function.⁴⁰ Also it seems that parenting of children affects the HPA-axis reactivity to stress. A low structured approach to parenting induce higher HPA axis reactivity to stress.²¹ There are other studies associating high saliva cortisol levels with suicide and social phobia, but none clear up the mechanism of this relationship. Also it was found that oxytocin increased and oxytocin inhibition decreased spatial memory and L-LTP, through MAP-kinases and CREB elements. This was displayed by injection of oxytocin and oxytocin antagonist in the hippocampus of maternal mice.³⁴ These are just small steps towards understanding this relationship and a clear cut answer is still not attainable. It is hard to research mechanism behind these social behavior patterns because it can only be done in humans and therefore methods for research are limited.

Oxytocin regulate social behavior and depression

Is oxytocin's effect on social recognition and trust related to depression? Can changes in these social behavioural patterns decrease depression related behavior? Oxytocin influences different regions in the brain which are responsible for social recognition, bonding and trust like the prefrontal cortex and these are closely related to anxiety.^{29, 31, 42} The possibility arises that these proprieties of the brain interact and we come to a quite logical but speculative conclusion that anxiety decreases trusting and bonding behavior. These effects might be partly due to the mechanism uncovered above. This means that ERK1/2 activation and decrease in anxiety that arises will increase trusting and bonding behavior. Even if that were true, it still isn't clear whether increased trust and bonding can reverse the trend toward social isolation and disregard seen in depression.

Can Oxytocin function as antidepressant?

HPA hyperactivity a clear state in depression

It is clear that a hyperactivity of the HPA axis coincides with depression. An overactive stress mechanism may lead to many of the effects generally known to be present in depressed patients. The hyperactivity of the HPA is most likely the cause of a high secretion of CRH in the brain, but this doesn't necessarily have to be the cause for high HPA activity. A malfunctioning feedback may also cause an increase in CRH secretion. This may also involve different transcriptional mechanisms, like ERK and downstream CREB, through which feedback loops might function.

CRH hyperdrive cause or effect

The CRH hyperdrive in depressed patients seem to be a clear point to interrupt the hyperactivity of the HPA axis in depressed patients. If this can reduce depression remains to be seen. High CRH levels might be an expression of depression, the depression itself may be caused in other part of the brain. Considering that anxiety is also a large factor in being depressed, anxiety might also trigger HPA hyperactivity and cause the CRH hyperactivity. Stress activity is known to be triggered by emotional impulse like anxiety. A persistent anxiety impulse might also trigger a constantly increased HPA activity. Even though CRH is known to trigger anxiety and it might as well be the other way around, CRH the chicken or the egg. Central administration of CRH antagonists should reveal whether CRH suppression can alleviate the symptoms of depression that CRH is associated with.

Oxytocin as HPA modulator

Both in the periphery as well as centrally oxytocin suppress the HPA after stress induced HPA hyperactivity. Oxytocin seems to also have an effect on basal HPA activity but it is unclear whether it suppresses or increases HPA activity at a basal level. The fact that oxytocin modulates the HPA centrally as well as peripherally indicates that it modulates glucocorticoid secretion at the level of ACTH effectiveness as well as in the secretion of CRH in the brain. The influence of oxytocin in PVN revealed by antagonist studies,¹⁷ might not be as reliable as it seems. As the PVN is responsible for most of the homeostasis of hormone levels, blocking oxytocin receptors might elicit a release of oxytocin into the blood. The reduction in HPA activity might well be caused by peripheral oxytocin and not directly by a reduction of CRH secretion.

Oxytocin is clearly a modulator of the HPA axis, and in general administration reduces the response of the HPA to stress. This reduction may well be mediated through many different parts of the brain. Modulation of the HPA and behavior might work through many parts of the brain, since oxytocin receptors are widely expressed. Regulation of anxiety related and social behavior might even be directly regulated by modulation of HPA-axis or vice-versa.

Oxytocin regulates anhedonia and anxiety through modulation of HPA-axis and ERK

It is clear that oxytocin administration in the hypothalamic region and centrally is anxiolytic. In hypothalamus and medial prefrontal cortex this works through ERK1/2 MAP kinase activation.³¹ It has been demonstrated quite clearly that oxytocin anxiolytic effect is related to lower activation of CRH neurons in the PVN.¹⁸ The effects found by Blume et al are quite likely, at least partly, to be due to attenuation of CRH neurons, especially because ERK1/2 have been demonstrated to regulate

CRH expression in CRH neurons. ERK 1/2 activation in the dorsal hippocampus and medial prefrontal cortex have are directly linked to depressed behavior, but there is a bit of a disputed on the effect of ERK1/2 on the depressed behavior. Also CRH can decrease ERK/1/2 activation so there is clearly a feedback loop involved in this way of CRH secretion. Todorovic et al. found that ERK1/2 deactivation lead to decreased depressed behavior in CRH knockout mice, while Qi et al. found that ERK1/2 deactivation and CREB deactivation increased depressed behavior in through perfusion of MEK-inhibitor in specific parts of the brain. However the methods of Todorovic et al. are systemic and CRH receptor are distributed widely in the brain the effect on anxiety in knock out mice could work through many different pathways which CRH influences. Qi et al targeted the dorsal hippocampus and medial prefrontal cortex specifically which give a better understanding of the functional background. Also Todorovic et al. used the forced swim and saccharine preference test paradigms for depression and Qi et al. the open armed plus maze and light box paradigms. Forced swimming, helplessness behavior and saccharine preference tests provide insight into anhedonia of animals, while the open armed plus maze and light box paradigms are more focused on anxiety. Qi et al. contested Todorovic results in the same paradigm with the positive control of fluoxetine, showing that saccharine preference test and forced swim test showed an increase in depressed behavior due to ERK1/2 deactivation. This effect was reversed by fluoxetine treatment.³⁶⁻³⁸ As CRH knock-out rats have a systemic deficiency it is hard to elucidate the mechanisms of action, making Qi et al. approach a lot more elegant and feasible. Todorovic states that he finds a reduction in depressed behavior in the forced swim and tail suspension test, while it is stated that the forced swim and tail suspension test is not a measure for depressed behavior but can test antidepressant effects. Only after repeated subject to these test is may be a measure for depressed behavior.⁴³

In humans the ERK1/2 cascades is less active in depressed patient, which makes the translation of the result in from the rat model to humans feasible, especially because the SSRI fluoxetine is used in humans and has been show to reverse this deactivation. Through ERK1/2 a mechanism becomes apparent, through which oxytocin can manifest its anxiolytic effect possibly by modulation of the HPA-axis. A scheme of this system is shown in figure 13. This might be a target to develop new therapeutic strategy and antidepressants

Social behavior regulated by HPA-axis reactivity

In the end does it come down to HPA-axis reactivity? It may very well do. There is a clear cut relationship between HPA-axis hyperactivity in response to stress and depression. Early life events and genetics can regulate the HPA-axis reactivity to stress and increase prevalence of depression to occur. So far interference in this mechanism has only been successful in the form of SSRI, as it becomes more apparent SSRI's mode of action is most likely through modulation of CREB activity, at least partly by ERK1/2 activation. A more direct approach at regulating this system has been regarded as a good target for more effective anti-depressants. It might even be possible that the effect of oxytocin on social behavior is also mediated by the HPA-axis, as studies are indicating a relationship between HPA-axis reactivity/activity and social behavior. Oxytocin has its anxiolytic effect through areas of the brain like the prefrontal cortex, which are responsible for social cognition, trust and bonding. These facts make it interesting to see if currently understood mechanisms of

oxytocin, like attenuation of anxiety, can be linked to the prevalence of these social behavioural patterns.

Can oxytocin function as antidepressant?

Oxytocin might provide a more direct and effective mode of action to interfere with abnormalities in the CRH and ERK regulated mechanism. However the way that these mechanisms influence each other is not clear. Oxytocin might reduce CRH secretion by modulating the ERK/1/2 cascades, but it might as well be that oxytocin doesn't target CRH for its anxiolytic effect and further exploration is needed. Still if we accumulate the effect of oxytocin on anxiety and social behavior, oxytocin provides a very wide mode of action toward symptoms of depression. It might even be possible that the effect of oxytocin on social behavior is also mediated by the HPA-axis, as a few studies are indicating a relationship between HPA-axis reactivity/activity and social behavior. As it becomes more and more clear that the antidepressant effect of modern SSRI's is not mediated by the serotonin neurons but more likely through modulation of the CREB transcription factor by ERK1/2 activation, it become clear that this route through SSRI's is not very quick or effective. Oxytocin might provide a much more direct route through regulation of anxiety related behavior and activation of ERK1/2. Oxytocin can activate this system in combination with a wider array of positive effects on social and non-social behavior patterns that are still relatively unrelated to HPA-axis activity.

Oxytocin can interrupt the HPA-axis hyperactivity and related pathological behavior patterns and this warrants a thorough investigation on the effect of oxytocin in depressed patients. Oxytocin might provide a new and low risk alternative to current antidepressants like SSRI's which have a disputable and limited effect on depression. Further clarification of relationship between social behavior modulated by oxytocin and depression is needed to unveil if social isolation and disregard in depression can be decrease by inducing trust and bonding through oxytocin administration. Also the underlying mechanism for the increase trust and bonding behavior caused by oxytocin needs closer examination to see if this is linked to anxiety and its underlying mechanisms.

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