Stress
The International Journal on the Biology of Stress

ISSN: 1025-3890 (Print) 1607-8888 (Online) Journal homepage: informahealthcare.com/journals/ists20

The Activity of the Hypothalamo-Neurohypophysial System in Response to Acute Stressor Exposure: Neuroendocrine and Electrophysiological Observations

Mario Engelmann & Mike Ludwig

To cite this article: Mario Engelmann & Mike Ludwig (2004) The Activity of the Hypothalamo-Neurohypophysial System in Response to Acute Stressor Exposure: Neuroendocrine and Electrophysiological Observations, Stress, 7:2, 91-96, DOI: 10.1080/10253890410001677240

To link to this article: https://doi.org/10.1080/10253890410001677240

Stress, June 2004 Vol. 7 (2), pp. 91–96

Taylor & Francis
healthsciences

The Activity of the Hypothalamo-Neurohypophysial System in Response to Acute Stressor Exposure: Neuroendocrine and Electrophysiological Observations

MARIO ENGELMANN[a,*] and MIKE LUDWIG[b]

[a]*Otto-von-Guericke-Universität Magdeburg, Institut für Medizinische Neurobiologie, Leipziger Str. 44, D-39120 Magdeburg, Germany;* [b]*University of Edinburgh, Division of Biomedical Sciences, George Square, Edinburgh EH8 9XD, UK*

(Received 14 October 2003; Revised 31 January 2004; In final form 16 February 2004)

The present mini review focuses on stress-induced alterations of the electrical and secretory activity of vasopressin (AVP) and oxytocin (OXT) neurones originating within the supraoptic nucleus (SON) and constituting the hypothalamo-neurohypophysial system (HNS) in the male rat. Previously, it was thought that SON neurones are predominantly activated by osmotic and reproductive stimuli. However, recent findings also suggest a selective activation of AVP and/or OXT neurones in response to specific stressors. Inhibitory amino acids seem to participate at the level of the SON in the control of HNS activity during stress. Taurine, probably of glial origin, selectively inhibits the secretory activity of AVP neurones. In contrast, GABA, probably of neuronal origin, interferes with the release of OXT both from axon terminals into blood and from somata/dendrites into the extracellular fluid of the SON. Depending upon whether a defined stressor triggers taurine and/or GABA release within the SON the secretion of AVP and/or OXT from HNS neurones will be inhibited. These observations shed new light on the neurone–neurone and glial–neurone interactions that ensure an appropriate neuroendocrine stress response.

Keywords: Dendritic release; Forced swimming; Gamma-amino butyric acid; Oxytocin; Vasopressin; Social defeat; Taurine

INTRODUCTION

Previous studies showed that the magnocellular neurones of the supraoptic (SON) and paraventricular nuclei (PVN) are not only activated by osmotic and reproductive stimuli but also during stress. This conclusion is primarily drawn from recent findings indicating release of vasopressin (AVP) and oxytocin (OXT) from the somata and dendrites within the SON rather than from observations of AVP and OXT secreted from the posterior pituitary into the blood (Wotjak *et al.*, 1998; Engelmann *et al.*, 1999). Reports about somatic/dendritic release of AVP and OXT are based on microdialysis experiments which allow us to monitor local release profiles of potential neurotransmitters/neuromodulators within distinct brain areas in freely moving rats. In this context we have previously demonstrated that somatic/dendritic release of AVP and OXT during a 10-min forced swimming session differs considerably from that during a 30-min social defeat experience. Whereas OXT release within the SON is increased in response to both stressors, AVP release was found to be triggered by forced swimming only (Wotjak *et al.*, 1998). Both social defeat and forced swimming increase plasma corticotropin (ACTH) and corticosterone (Cort) levels indicating an activated hypothalamic–pituitary–adrenal (HPA) axis (Wotjak *et al.*, 1996; 1998). Thus, both stimuli qualify as stressors and fulfil the criteria of being physiologically and ethologically relevant.

METHODOLOGICAL CONSIDERATIONS

It is well known that parturition and lactation change the morphology of the SON which affects the electrophysiological and neurosecretory properties of magnocellular neurones (for review see Theodosis *et al.*, 1995). Thus, we used adult male or (in only one case) virgin female albino rats in our studies (body mass between 200 and 400 g). The rats were exposed to the stressors between

*Corresponding author. Tel.: +49-391-67-14363. Fax: +49-391-67-14365. E-mail: mario.engelmann@medizin.uni-magdeburg.de

ISSN 1025-3890 print/ISSN 1607-8888 online © 2004 Taylor & Francis Ltd
DOI: 10.1080/10253890410001677240

9:00 and 14:00 h during the day time (housing conditions: 12-h light: dark cycle with lights on at 07.00 h). The studies presented here were performed with local ethical committee approval and in accordance with German and UK Government Regulations.

In our studies, forced swimming was performed by transferring rats from their home cage to a Plexiglas cylinder (50 cm high; 30 cm in diameter) filled with tap water of approx. 20°C (depth approx. 35 cm) and forcing them to swim for 10 min. For the social defeat procedure, the experimental rat (intruder) was introduced into the home cage of another rat (resident) and behavioural posture and ultrasonic vocalisation were recorded. Immediately after the first successful defeat of the intruder, the rats were separated by a wire mesh barrier that allowed further exchange of visual, olfactory and acoustic signals between the animals but prevented physical contact. This procedure was chosen to emphasize the emotional and minimize the physical aspect of the stress. Typically, the resident continued to display threatening postures after separation from the intruder. After 30 min the experimental rat was returned to its home cage.

For the *in vivo* electrophysiological studies (Ludwig and Leng, 1997) magnocellular neurosecretory neurones were identified by antidromic stimulation from the neural stalk. OXT and AVP neurons are intermingled in the SON, but they are distinguishable from each other by both their firing pattern and response to intravenously administered cholecystokinin; i.e. transient excitation by cholecystokinin of OXT neurones (Renaud *et al.*, 1987) and no effect or short-term inhibition of AVP neurones (Leng *et al.*, 1991). AVP neurone discharge activity consists typically of alternating periods of activity and silence lasting tens of seconds each (phasic firing) whereas OXT neurones in male or virgin animals never discharge phasically but typically discharge continuously at between 1 and 5 spikes/s.

REGULATION OF THE ACTIVITY OF AVP AND OXT NEURONES IN THE SON DURING FORCED SWIMMING AND SOCIAL DEFEAT

We have shown that *forced swimming* stimulates the release of OXT and AVP within the SON, however, only OXT and not AVP levels were increased in the plasma (Tables I and II; Wotjak *et al.*, 1998). In contrast, *social defeat* failed to alter plasma OXT although extracellular OXT levels within the SON were increased. The same stressor changed neither plasma levels nor somatic/dendritic release of AVP (Tables I and II; Engelmann *et al.*, 1999). As these results suggested that both AVP neurones (during forced swimming) and OXT neurones (during social defeat) are able to release their nonapeptides from different parts of their cell membrane independently, the question arose as to what might be the regulatory mechanisms that control this dissociation.

TABLE I Effects of stressor exposure on the release of AVP and OXT from the axon terminals of HNS neurones in the posterior pituitary gland into blood

Stressor	AVP	OXT
Social defeat	○	○
Forced swimming	○*	↑

*: AVP is released within 1 min after stressor exposure and returns to basal levels after 2 min (see Fig. 2). ↑: increase, ○: no change (data compiled from Engelmann *et al.*, 1999; Wotjak *et al.*, 1996, 1998).

We speculated that these mechanisms act within the SON at the somatic/dendritic level and should involve modulation of electrical and secretory activity. To test this hypothesis a series of experiments was performed in which microdialysis was combined with either blood sampling via chronically implanted catheters in freely moving rats or with *in vivo* electrophysiology in urethane-anesthetised animals. As a first step, the release of excitatory and inhibitory amino acids within the SON in response to the above stressors was monitored by microdialysis in conjunction with high performance liquid chromatography. During forced swimming we found increased levels of aspartate, glutamate and taurine but, surprisingly, not GABA. Whereas aspartate and glutamate are released from neurones and provide an excitatory input to the SON (Iijima *et al.*, 1986; Theodosis *et al.*, 1986; Meeker *et al.*, 1989, 1993; Herbison, 1994; Schell *et al.*, 1997), taurine most likely originates from glial cells of the ventral lamina (Decavel and Hatton, 1995; Deleuze *et al.*, 1998) and is known to inhibit magnocellular neurones within the SON (Deleuze *et al.*, 1998; Hussy, 2002). Despite enhanced activity of excitatory inputs to SON neurones, plasma AVP concentrations remained unchanged in response to forced swimming. Thus, the observed increase in taurine, but not GABA, release within the SON suggested that taurine could act locally to suppress secretion of AVP into blood. To test this hypothesis we administered a selective taurine antagonist via retrodialysis into the SON to interfere with taurine signalling during forced swimming. Taurine antagonist treatment triggered the release of AVP both into blood and from within the SON, from somata/dendrites (Fig. 1), without affecting OXT levels in either compartment under resting conditions (Table III; Engelmann *et al.*, 2001). It is important to note that the taurine antagonist has to compete with the increased extracellular taurine concentration during forced swimming (Engelmann *et al.*, 2001).

TABLE II Effects of stressor exposure on the release of AVP and OXT from somata/dendrites of HNS neurones within the SON

Stressor	AVP	OXT
Social defeat	○	↑
Forced swimming	↑	↑

↑: increase, ○: no change (data from Engelmann *et al.*, 1999; Wotjak *et al.*, 1996, 1998).

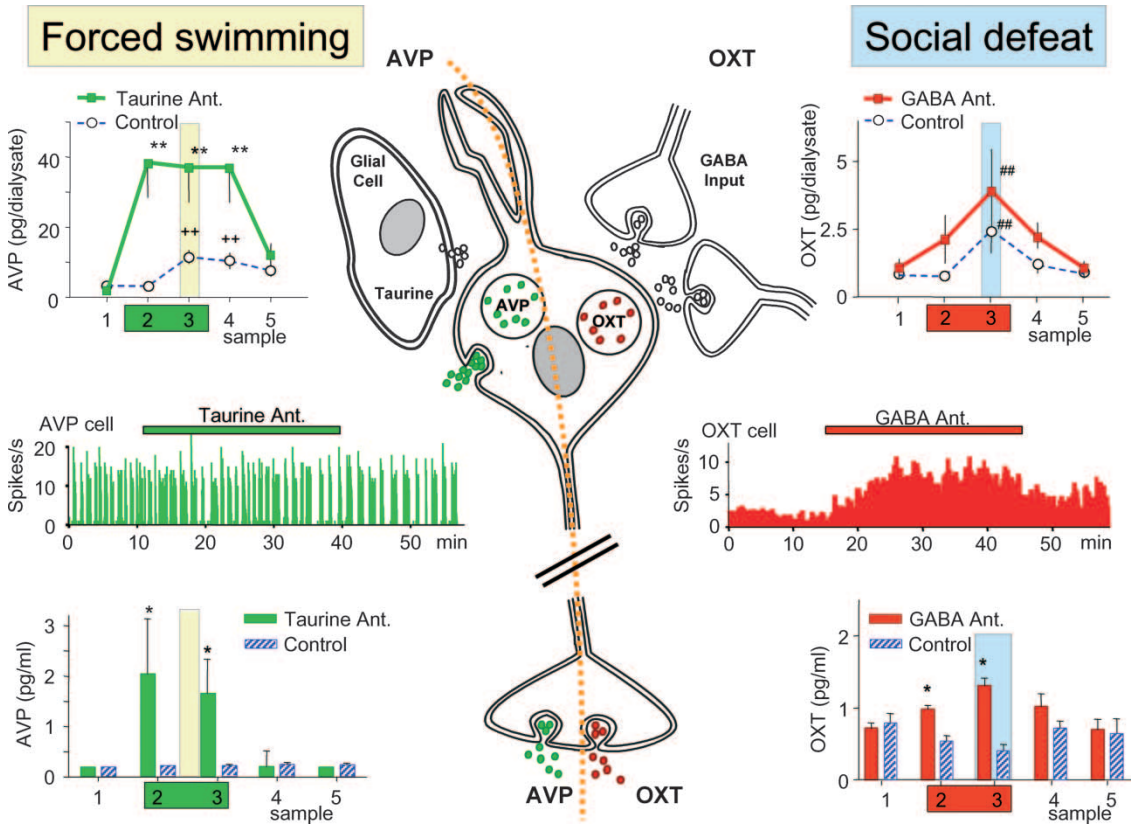

FIGURE 1 Selective inhibition of SON AVP neurones by taurine and of OXT neurones by GABA, as revealed by antagonist treatment during stressor exposure. Rats were implanted with microdialysis probes to administer the antagonists via retrodialysis into the SON before and during forced swimming (left panel) and social defeat (right panel). Upper panel: Microdialysis treatment with the taurine antagonist (taurine ant; 6-aminomethyl-3-methyl-4H-1,2,4-benzothiadiazine-1,1-dioxide; Left, green box) triggered the release of AVP within the SON before, during and after forced swimming (yellow bar). Treatment with the GABA antagonist bicuculline (GABA Ant; Right, red box) increased the somatic/dendritic release of OXT (samples collected over 30 min intervals) without stressor exposure, and tended to further increase it during social defeat (light blue bar). $^{**}p < 0.01$ vs. sample 1 and all control samples;$^{++}p < 0.01$ vs. sample 1; $^{\#\#}p < 0.01$ vs. sample 1. Middle panel: Microdialysis administration into the SON in anaesthetized rats of (left) the taurine antagonist increased the electrical activity (increase in burst duration) of identified AVP neurones, and (right) the GABA antagonist excited OXT neurones (increase in mean firing rate). Lower panel: The taurine antagonist also increased plasma AVP concentration, whereas the GABA antagonist increased plasma OXT concentration. Blood samples were collected 35 and 5 min before as well as 15, 55 and 85 min after onset of the stressor. $^{*}p < 0.05$ vs. sample 1 and control samples at same time (modified from Engelmann *et al.*, 2001, 2004).

TABLE III Effects of taurine antagonist and GABA antagonist administration directly into the SON on different parameters associated with the release of AVP and OXT from HNS neurones compared to untreated conditions

		AVP release/AVP neurone activity		OXT release/OXT neurone activity	
	Parameter	Without stressor	Stressor exposure	Without stressor	Stressor exposure
Taurine antagonist	SON extracellular concentration	↑	↑	○	?
	Spike/s	↑	?	○	?
	Plasma concentration	↑	↑	○	○
GABA antagonist	SON extracellular concentration	?	?	↑	↑*
	Spike/s	○	?	↑	?
	Plasma concentration	○	○	↑	↑*

↑: increase compared with untreated, no significant difference between without stressor and stressor exposure; *: tendency to further increase compared to without stressor conditions; ○: no change; ?: not determined/not measurable (data from Engelmann *et al.*, 2001, 2004).

Additionally, as already mentioned, defined stressor exposure triggers the release of the excitatory amino acids glutamate and aspartate. This illustrates the complexity of the regulatory mechanisms active during forced swimming involved in controlling the activity of hypothalamo-neurohypophysial system (HNS) neurones at the level of the SON. Obviously, antagonist effects obtained during this scenario can hardly be compared with those under resting conditions. This might explain why we failed to measure during stressor exposure a further increase of AVP levels due to antagonist treatment. In any case, the present results suggest that taurine participates significantly in the inhibitory mechanisms, acting at the level of the SON, to selectively control the secretory activity of AVP neurones. Indeed, combined retrodialysis and *in vivo* electrophysiology confirmed that taurine antagonist administration increased the electrical activity of AVP but not OXT neurones within the SON (Engelmann *et al.*, 2001).

The results obtained during forced swimming are consistent with the hypothesis that, as for taurine and AVP, there is also a selective inhibitory mechanism for OXT neurones acting at the level of the SON. In contrast to forced swimming, we observed a release of OXT within the SON but not into blood in response to social defeat. The release patterns of excitatory and inhibitory amino acids within the SON in response to social defeat were monitored via microdialysis and demonstrated an increased release of glutamate, taurine and GABA, but not of aspartate. To investigate the consequences of the increased GABA release on the secretion of both AVP and OXT neurones, we administered the $GABA_A$ receptor antagonist bicuculline via retrodialysis into the SON concomitantly with a social defeat experience. Bicuculline treatment caused a significant increase of OXT plasma levels and triggered the release of OXT within the SON (Fig. 1). In contrast, AVP plasma concentrations remained unchanged (Table III). Again, antagonist treatment effects during stressor exposure are likely to be affected by the various regulatory mechanisms activated to control HNS neurone activity which make it difficult to simply extrapolate from resting conditions. More insight in the differences between resting conditions and stressor exposure could have been provided by measurement of AVP levels in microdialysates obtained from the SON. Unfortunately, the effects of bicuculline treatment on somatic/dendritic AVP concentrations could not be measured as bicuculline interfered with the AVP radioimmunoassay (Engelmann *et al.*, 2004).

The findings concerning the effects of bicuculline treatment on HNS neuronal secretion were extended by *in vivo* electrophysiology in anaesthetised rats. Retrodialysis of bicuculline of the same dosage as used above increased the electrical activity of OXT, but not AVP, neurones (Fig. 1; Engelmann *et al.*, 2004), while higher doses of bicuculline also stimulated the electrical activity of AVP neurones (Ludwig and Leng, 2000). These results require cautious interpretation as higher doses have been shown to induce cramps and barrel rotations in freely moving animals if administered into the PVN area (Engelmann, unpublished observations), implying disinhibition of GABAergic inputs distal to the site of administration. Superficially, the selective action of a $GABA_A$ receptor antagonist on OXT neurons contrasts with findings published by Moos (1995) obtained with lactating females. However, as stated above parturition and lactation alter both the morphology of the SON (for review see Theodosis *et al.*, 1995) and the electrophysiological properties of magnocellular neurons compared with male or virgin female rats (Stern and Armstrong, 1996). Thus, our data are consistent with the hypothesis that GABAergic neurotransmission in the SON may change during reproductive states.

Additional experiments were performed to investigate whether forced swimming exposure induces a rapid and transient increase in plasma AVP levels that we might have missed with our previous sampling protocol (Hashimoto *et al.*, 1989). Plasma samples were collected from stressed rats chronically fitted with jugular venous catheters. To our surprise we measured significantly increased plasma AVP levels one minute after onset of the stressor which returned another minute later to basal levels (Fig. 2). One possible explanation for this transient increase in plasma AVP level may involve the signalling characteristics of taurine. In contrast to glutamate and aspartate, both excitatory and of neuronal origin, taurine is released from glial cells. It may be that exposure to forced swimming immediately activates fast synaptic glutamate and aspartate inputs to the SON neurones whereas taurine, because of its release from glial cells, reaches levels that suppress AVP neuronal activity only two minutes later. The hypothesis of a delay in the inhibitory action of taurine due to its non-synaptic release is supported by the results of an experiment in which we investigated possible fast changes in plasma OXT in response to social defeat. Following a similar protocol used during forced swimming, we failed to detect significant changes in plasma OXT at any of the time points investigated. This implies that GABA, because of its neuronal origin, provides a synaptic inhibition of OXT neurones that seems to be at least as fast as the neuronal excitatory inputs e.g. via glutamate. As a consequence, there is no transient release of OXT into the plasma.

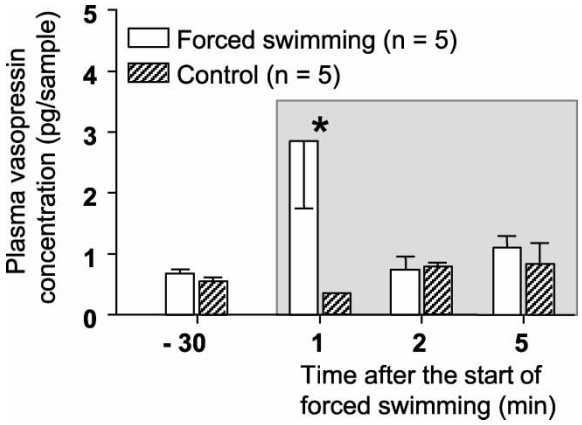

FIGURE 2 *Rapid but transient effect of forced swimming on the release of AVP into plasma*. Rats were implanted with chronic jugular venous catheters. On the day of experiment, blood samples were withdrawn from the unrestrained rats for measurement of AVP as described elsewhere (Wotjak *et al.*, 1998). Blood samples were collected 30 min before and 1, 2, and 5 min after onset of forced swimming (grey box). $*p < 0.05$ vs. all other samples.

CONCLUSION

Taken together our findings suggest that, depending upon the specific stressor applied, HNS neurones are activated at different levels. Forced swimming triggered the release of OXT into blood. The role that OXT might play after its release into blood in male rats is not yet fully understood, but the regulation of glucocorticoid release and, thus, the activity of the HPA axis has been suggested

(Legros and Ansseau, 1992; Legros, 2001). Interestingly, we failed to see an increased release of OXT into blood during social defeat. This finding contradicts not only the hypothesis that OXT is a stress hormone in the rat (Lang *et al.*, 1983) but also, that circulating OXT has a generalised role to maintain the animal's homeostasis (Legros and Ansseau, 1992; Legros, 2001). Obviously, forced swimming differs significantly from social defeat in many respects. Each of the two stressors consists of a different orchestra of sensory stimuli, and there were differences in the duration of stressor exposure. It is likely that these variables contribute to the activation of different control mechanisms at the level of the SON and, thus, the different release patterns of OXT into blood and brain between forced swimming and social defeat. Further studies are required to evaluate in more detail how the balance between physical and emotional stimulation determines the control of OXT and AVP release.

Interestingly, except for the transient increase in plasma AVP level during forced swimming, we failed to observe elevated plasma AVP levels in response to exposure to either stressor. In fact, except for only a few stimuli, including body compression (Husain *et al.*, 1979) and ether exposure (Hashimoto *et al.*, 1989), plasma AVP levels in the rat remain stable or even show reduced levels during stress (Yagi, 1992). Apparently, the mechanisms controlling AVP neurones are set to avoid high plasma AVP levels during stress. One possible advantage may be that, because AVP released from the neurohypophysis stimulates ACTH secretion (Wotjak *et al.*, 2002), a strict control of the secretory activity of AVP neurones would avoid an overshoot of HPA axis activity. Interestingly, within the SON, AVP itself seems to contribute to this inhibitory control. After being released from somata/dendrites, AVP inhibits its own release into the blood (Ludwig and Leng, 1997) and facilitates the return of the HPA axis activity to basal levels (Wotjak *et al.*, 2002). The attempt to strictly control plasma AVP levels might also explain the existence of further inhibitory mechanisms at the level of the neurohypophysis that, in addition to those within the SON, restrict the release of AVP into blood (Hussy *et al.*, 2001). Again, we suggest that because this local inhibitory mechanism acts via taurine released from glial cells (pituicytes) in a non-synaptic manner, this might explain why it is not sufficient to suppress the transient increase in plasma AVP in response to forced swimming (Fig. 2).

In addition to the activity of neurones in the SON, the release of both AVP and OXT were monitored within the PVN. Exposure to social defeat resulted in an increased AVP but not OXT release within this nucleus (Wotjak *et al.*, 1996), while during forced swimming both AVP and OXT were released (Wotjak *et al.*, 1998). These data suggest that magnocellular PVN and SON neurones are not activated equally. Furthermore, as suggested previously (Wotjak *et al.*, 1996), intra-PVN release of AVP seems to reduce the activity of the HPA axis. Proposed mechanisms include the interaction of AVP released from somata and dendrites of magnocellular neurones acting at receptors on parvocellular PVN neurones to reduce the secretion of the corticotropin releasing hormone and AVP into the hypothalamo-hypophysial portal blood. To test this hypothesis with *in vivo* electrophysiology is a challenge that would provide further clarification of the interaction between the HNS and HPA axis that results in an appropriate stress response by the organism.

Acknowledgements

The study was supported by grants from *Deutsche Forschungsgemeinschaft* (SP672/1-1, ME), the Wellcome Trust and BBSRC (ML).

References

Decavel, C. and Hatton, G.I. (1995) Taurine immunoreactivity in the rat supraoptic nucleus: prominent localization in glial cells, *J. Comp. Neurol.* **354**, 13–26.

Deleuze, C., Duvoid, A. and Hussy, N. (1998) Properties and glial origin of osmotic-dependent release of taurine from the rat supraoptic nucleus, *J. Physiol.* **507**, 463–471.

Engelmann, M., Ebner, K., Landgraf, R., Holsboer, F. and Wotjak, C.T. (1999) Emotional stress triggers intrahypothalamic but not peripheral release of oxytocin in male rats, *J. Neuroendocrinol.* **11**, 867–872.

Engelmann, M., Ludwig, M., Singewald, N., Ebner, K., Sabatier, N., Lubec, G., Landgraf, R. and Wotjak, C.T. (2001) Taurine selectively modulates the secretory activity of vasopressin neurons in conscious rats, *Eur. J. Neurosci.* **14**, 1047–1055.

Engelmann, M., Bull, P.M., Brown, C.H., Landgraf, R., Horn, T., Singewald, N., Ludwig, M. and Wotjak, C.T. (2004) GABA selectively controls the secretory activity of oxytocin neurons in the rat supraoptic nucleus, *Eur. J. Neurosci.* **19**, 601–608.

Hashimoto, K., Murakami, K., Takao, T., Makino, S., Sugawara, M. and Ota, Z. (1989) Effect of acute ether or restraint stress on plama corticotropin-releasing hormone, vasopressin and oxytocin levels in the rat, *Acta Med. Okayama* **43**, 161–167.

Herbison, A.E. (1994) Immunocytochemical evidence for oestrogen receptors within GABA neurones located in the perinuclear zone of the supraoptic nucleus and GABAA receptor beta 2/beta 3 subunits on supraoptic oxytocin neurones, *J. Neuroendocrinol.* **6**, 5–11.

Husain, M.K., Manger, W.M., Rock, T.W., Weiss, R.J. and Frantz, A.G. (1979) Vasopressin release due to manual restraint in the rat: role of body compression and comparison with other stressful stimuli, *Endocrinology* **104**, 641–644.

Hussy, N. (2002) Glial cells in the hypothalamo-neurohypophysial system: key elements of the regulation of neuronal electrical and secretory activity, *Prog. Brain Res.* **139**, 95–112.

Hussy, N., Bres, V., Rochette, M., Duvoid, A., Alonso, G., Dayanithi, G. and Moos, F.C. (2001) Osmoregulation of vasopressin secretion via activation of neurohypophysial nerve terminals glycine receptors by glial taurine, *J. Neurosci.* **21**, 7110–7116.

Iijima, K., Ohtomo, K., Kobayashi, R. and Kojima, N. (1986) Immunohistochemical studies on the GABAergic system in the rat supraoptic nucleus using the PAP method with an application of electron microscopy, *Arch. Histol. Jpn.* **49**, 579–591.

Lang, R.E., Heil, J.W., Ganten, D., Hermann, K., Unger, T. and Rascher, W. (1983) Oxytocin unlike vasopressin is a stress hormone in the rat, *Neuroendocrinology* **37**, 314–316.

Legros, J.J. (2001) Inhibitory effect of oxytocin on corticotrope function in humans: are vasopressin and oxytocin ying-yang neurohormones?, *Psychoneuroendocrinology* **26**, 649–655.

Legros, J.J. and Ansseau, M. (1992) Neurohypophyseal peptides and psychopathology, *Prog. Brain Res.* **93**, 455–460.

Leng, G., Way, S. and Dyball, R.E. (1991) Identification of oxytocin cells in the rat supraoptic nucleus by their response to cholecystokinin injection, *Neurosci. Lett.* **122**, 159–162.

Ludwig, M. and Leng, G. (1997) Autoinhibition of supraoptic nucleus vasopressin neurons *in vivo*: a combined retrodialysis/electrophysiological study in rats, *Eur. J. Neurosci.* **9**, 2532–2540.

Ludwig, M. and Leng, G. (2000) GABAergic projection from the arcuate nucleus to the supraoptic nucleus in the rat, *Neurosci. Lett.* **281**, 195–197.

Meeker, R.B., Swanson, D.J. and Hayward, J.N. (1989) Light and electron microscopic localization of glutamate immunoreactivity in the supraoptic nucleus of the rat hypothalamus, *Neuroscience* **33**, 157–167.

Meeker, R.B., Swanson, D.J., Greenwood, R.S. and Hayward, J.N. (1993) Quantitative mapping of glutamate presynaptic terminals in the supraoptic nucleus and surrounding hypothalamus, *Brain Res.* **600**, 112–122.

Moos, F.C. (1995) GABA-induced facilitation of the periodic bursting activity of oxytocin neurones in suckled rats, *J. Physiol.* **488**, 103–114.

Renaud, L.P., Tang, M., McCann, M.J., Stricker, E.M. and Verbalis, J.G. (1987) Cholecystokinin and gastric distension activate oxytocinergic cells in rat hypothalamus, *Am. J. Physiol.* **253**, R661–R665.

Schell, M.J., Cooper, O.B. and Snyder, S.H. (1997) D-aspartate localizations imply neuronal and neuroendocrine roles, *Proc. Natl Acad. Sci. USA* **94**, 2013–2018.

Stern, J.E. and Armstrong, W.E. (1996) Changes in the electrical properties of supraoptic nucleus oxytocin and vasopressin neurons during lactation, *J. Neurosci.* **16**, 4861–4871.

Theodosis, D.T., Paut, L. and Tappaz, M.L. (1986) Immunocytochemical analysis of the GABAergic innervation of oxytocin- and vasopressin-secreting neurons in the rat supraoptic nucleus, *Neuroscience* **19**, 207–222.

Theodosis, D.T., el Majdoubi, M., Gies, U. and Poulain, D.A. (1995) Physiologically-linked structural plasticity of inhibitory and excitatory synaptic inputs to oxytocin neurons, *Adv. Exp. Med. Biol.* **395**, 155–171.

Wotjak, C.T., Kubota, M., Liebsch, G., Montkowski, A., Holsboer, F., Neumann, I. and Landgraf, R. (1996) Release of vasopressin within the rat paraventricular nucleus in response to emotional stress: a novel mechanism of regulating adrenocorticotropic hormone secretion?, *J. Neurosci.* **16**, 7725–7732.

Wotjak, C.T., Ganster, J., Kohl, G., Holsboer, F., Landgraf, R. and Engelmann, M. (1998) Dissociated central and peripheral release of vasopressin, but not oxytocin, in response to repeated swim stress: new insights into the secretory capacities of peptidergic neurons, *Neuroscience* **85**, 1209–1222.

Wotjak, C.T., Ludwig, M., Ebner, K., Russell, J.A., Singewald, N., Landgraf, R. and Engelmann, M. (2002) Vasopressin from hypothalamic magnocellular neurons has opposite actions at the adenohypophysis and in the supraoptic nucleus on ACTH secretion, *Eur. J. Neurosci.* **16**, 477–485.

Yagi, K. (1992) Suppressive vasopressin response to emotional stress, *Jpn. J. Physiol.* **42**, 681–703.