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STUDIES ON THE VASOPRESSIN AND OXYTOCIN STORAGE IN THE HYPOTHALAMUS AND NEUROHYPOPHYSIS*.

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The hypothalamic vasopressinergic and oxytocinergic neurones are known to be the „common final path” of neurohumoral reflexes related to the synthesis and release of neurohypophysial hormones [Hayward, 1972]. The neural input to these neurones is determined by afferent impulses born in central detectors, peripheral receptors and some central structures (e.g., the limbic system). Monoaminergic (adrenergic, noradrenergic, dopaminergic) and cholinergic units are thought to be included in respective multineuronal chains [Sklar and Schrier, 1983; Guzek, 1984]. Some putative neuromediators and/or neuromodulators (histamine, prostaglandins, angiotensin, substance P, bradykinin, cholecystokinin, GABA, glycine, etc) are supposed to be also involved in the events in question [Guzek, 1984; Sklar and Schrier, 1983].

Several physiological and pathological conditions do affect the synthesis and release of neurohypophysial hormones. In turn, the vasopressin and oxytocin storage in the hypothalamo-neurohypophysial system may be modified accordingly. Here we shall review our studies on bioassayed vasopressin and oxytocin storage as affected by some experimental conditions, the modified neurotransmission in the brain.

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being considered particularly. For the bioassay of vasopressin the method of Dekański (1952) was used; for that of oxytocin, the procedure of van Dongen and Hays (1966) was followed.

The hypothalamic and neurohypophysial vasopressor and oxytocic activities in stressed rats

It has been shown recently that the response of vasopressinergic and oxytocinergic neurones to stress varies qualitatively according to the kind of stressor: both vasopressin [Olczak and Guzek, 1983] and oxytocin [Guzek et al., 1984] neurohypophysial content decreased following immobilization but increased or did not change in rats exposed to cold. The beta-adrenergic blockade, brought about by using intraperitoneal (i.p.) injections of propranolol hydrochloride (1 mg/100 g b.w.) as pharmacological tool, did not influence the hypothalamic and neurohypophysial content of oxytocin under conditions of stress due to restraint or low environmental temperature. It follows therefore that under conditions of stress the modifications of oxytocin storage are probably independent from beta-adrenergic transmission [Guzek et al., 1984].

Further experiments were designed to evaluate the effects of alpha-adrenergic blockade; under treatment with phenoxybenzamine hydrochloride (0.2 mg/100 g i.p.) the vasopressin and oxytocin content in the neurohypophysis was diminished in stressed (both immobilized and cold-exposed) rats when compared with respective groups of untreated animals subjected to appropriate kind of stress. Thus, the alpha-adrenergic transmission seems to be somehow involved in the mechanisms of modified neurohypophysial function in stressed animals [Guzek et al., 1985].

The hypothalamic and neurohypophysial vasopressin and oxytocin storage as influenced by modified adrenergic transmission under various states of water metabolism

Rats dehydrated up to 8 days and subsequently rehydrated were given intracerebroventricularly (i.c.v.) methoxamine hydrochloride (MX) or dihydroergotamine methanesulphonate (DHE), each in a daily dose of 10 μg dissolved in 10 μl of 0.9 per cent sodium chloride. A single dose of MX injected to euhydrated animals increased the release of hypothalamic and neurohypophysial vasopressin but did not affect significantly the oxytocic activity in the hypothalamus and in the neurohypophysis. Under conditions of dehydration MX did not influence the hypothalamic vasopressin content but it stimulated the neurohypophysial vasopressin depletion. On the contrary, MX distinctly inhibited the decrease of hypothala-
mic and neurohypophysial oxytocin content in dehydrated animals. In rehydrated animals MX restrained the recovery of hypothalamic stores of vasopressin and oxytocin but intensified this process in the neurohypophysis [Ciosek et al., 1985].

A single dose of DHE decreased the vasopressin content in the hypothalamus as well as the oxytocin content both in the hypothalamus and neurohypophysis. Under conditions of dehydration DHE stimulated the depletion of hypothalamic vasopressin and oxytocin. On the contrary, this drug strongly inhibited the depletion of oxytocin in the neurohypophysis of dehydrated rats. DHE inhibited the recovery of hypothalamic vasopressin and oxytocin stores as well as intensified this process in the neurohypophysis of subsequently rehydrated rats [Ciosek et al., 1985].

These findings are consistent with previous data concerning the effects of modified alpha-adrenergic transmission on the synthesis and release of neurohypophysial hormones [for references see: Guzek et al., 1981]. Furthermore, the present experiments indicate that afferent impulses of osmoreceptor origin modify the functional responses of the vasopressinergic and oxytocinergic neurones to altered alpha-adrenergic transmission.

The effect of pinealectomy or melatonin on the hypothalamic and neurohypophysial content of vasopressin and oxytocin

In 1979 the diminution of bioassayed vasopressin in the neurohypophysis of pinealectomized rats was reported from this laboratory [Szczepanska-Szyburska et al., 1980; see also: Guzek, 1986]. These findings were soon confirmed; moreover, a decrease of bioassayed oxytocin in both hypothalamus and neurohypophysis was noted [Jusyczak and Guzek, 1983].

Desmethyldipramine hydrochloride (DMI; 20 \( \mu \)g i.c.v.) was reported to decrease the oxytocin content in the hypothalamo-neurohypophysial system of the rat [Guzek and Jusyczak, 1985]. In pinealectomized rats the oxytocin content in the hypothalamus and neurohypophysis, diminished following pineal removal, could be further reduced by an i.c.v. DMI injection. As shown in animals pretreated with phenoxybenzamine, this event was only partially related to an increase of alpha-adrenergic transmission [Guzek and Jusyczak, 1985].

Further experiments were designed to study the effects of beta-adrenergic blockade on the hypothalamic and neurohypophysial content of vasopressin and oxytocin in pinealectomized male rats; propranolol hydrochloride (1 mg/100 g b.w., i.p., once daily during five days) was used as pharmacological tool. Pinealectomy was followed by a decrease
of both vasopressin and oxytocin in the hypothalamus and neurohypophysis. In not pinealectomized rats, propranolol did not change the vasopressin and oxytocin content in the hypothalamo-neurohypophysial system. On the contrary, repeated administration of propranolol distinctly reversed the pinealectomy-induced decrease of hypothalamic and neurohypophysial vasopressin and oxytocin [Guzek and Juszczak, 1987].

The purpose of further study was to investigate the effects of melatonin on the oxytocin and vasopressin content in the hypothalamus and neurohypophysis of the rat. Melatonin injected in a single i.p. dose of 100 µg/100 g b.w. to euhydrated rats caused a decrease of neurohypophysial oxytocin content but the hypothalamic oxytocin storage as well as the hypothalamo-neurohypophysial storage of vasopressin were not changed. Following 8 days of once-daily melatonin treatment the hypothalamic and neurohypophysial oxytocin and vasopressin content was decreased [Juszczak et al., 1986]. It might be therefore suggested that melatonin increases the release of neurohypophysial hormones and/or decreases their synthesis. In order to see whether these effects might be modified by afferent impulses of osmoreceptor origin, a similar experimental protocol was also followed in dehydrated animals. Melatonin did not significantly modify the neurohypophysial vasopressin depletion rate in animals deprived of water up to eight days; it seems therefore that impulses born in osmoreceptors are of some importance for possible effects of melatonin on vasopressinergic neurones [Juszczak et al. 1986].

The effect of cholecystokinin on water intake and neurohypophysial storage of vasopressin and oxytocin

High concentration of cholecystokinin (CCK) in the hypothalamo-neurohypophysial system indicates a possible role of this neuropeptide in the release of neurohypophysial hormones. We studied the effects of CCK (Kabi, Studvik; this commercial preparation is a mixture of CCK-33 and CCK-39) on the neurohypophysial storage of vasopressin and oxytocin. i.c.v. injections of 10 ng CCK, once daily during four days, were followed by a decrease of vasopressin and oxytocin content in the neurohypophysis. Water intake and body weight diminished; serum osmolality and haematocrit index increased. All these effects — except the increase of haematocrit index — were more marked after eight days of daily i.c.v. treatment with CCK [Guzek and Morawska, 1986]. In this study the possible effect of CCK on susceptible units involved in afferent pathways converging on vasopressinergic and oxytocinergic neurones as well as the release of neurohypophysial hormones thereby altered should be taken into consideration. But it is possible as well that chronic
(4 or 8 days) administration of CCK primarily suppressed the mechanisms of thirst; the decrease of water intake might serve as starting point for subsequent events: negative water balance, stimulation of osmoreceptors and, finally, release of vasopressin and oxytocin [Guzek and Morawska, 1986].

**Summary and conclusions**

The effects of modified adrenergic transmission on the bioassayed storage of vasopressin and oxytocin in the hypothalamus and neurohypophysis under conditions of stress (cold or immobilization), disturbed water balance and pinealectomy are reviewed. Alpha-adrenergic mechanisms seem to be included in the response of vasopressinergic and oxytocinergic neurones to stress; on the other hand, impulses of osmoreceptor origin are of importance in regulatory processes affecting the functional response of these neurones to altered alpha-adrenergic transmission and also to melatonin. The beta-adrenergic (and, to some extent, also the alpha-adrenergic) transmission is probably involved in the neural mechanisms of the pineal-neurohypophysial relationship. Furthermore, a possible regulatory role of cholecystokinin in water metabolism and release of neurohypophysial hormones is suggested.

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