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OXYTOCIN AFFECTS UTILIZATION OF NORADRENALINE IN DISTINCT LIMBIC-FOREBRAIN REGIONS OF THE RAT BRAIN

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Summary—The effects of oxytocin, administered intracerebroventricularly in doses of 1, 10, 100 and 1000 pmol, were studied on the disappearance of catecholamines induced by α-methyl-*p*-tyrosine in microdissected nuclei of the rat brain. Oxytocin dose-dependently decreased the utilization of noradrenaline in the lateral and medial septal nuclei and anterior hypothalamic area, whereas an enhanced utilization was observed in the nucleus supraopticus. Tendency towards a change in utilization of noradrenaline was found in the dorsal septal nucleus and the lateral amygdala. Utilization of dopamine was not significantly affected in any of the nuclei of the brain studied. Tendency towards a decrease in utilization of dopamine was observed in the nucleus caudatus, globus pallidus and medial septal nucleus. It thus appears that oxytocin elicited changes in only a restricted number of brain nuclei. Interestingly, these nuclei contain cell bodies (nucleus supraopticus) and terminals (other nuclei) of the oxytocin system in the brain. Though the effects of oxytocin were not as widespread as those previously seen after administration of vasopressin, it is worthy of note that, in general, the effects of oxytocin were opposite to those seen after vasopressin. The opposite effecs of vasopressin and oxytocin on catecholamine metabolism could be related to the opposite effects of the two peptides on behaviour, neuroendocrine and autonomic regulation.

Key words: oxytocin, catecholamines, rat, brain.

Extensive neuronal networks have been identified in the brain with intra- and extrahypothalamic cell bodies and fibres containing vasopressin and oxytocin, projecting to the limbic system, medulla oblongata and the spinal cord (for a recent review see Buys, 1983). Both vasopressin and oxytocin have been found to be involved in the regulation of autonomic, neuroendocrine and behavioural processes (Van Ree, Bohus, Versteeg and De Wied, 1978; Kovacs, Bohus, Versteeg, Telegdy and De Wied, 1982; Kovacs and Telegdy, 1983; Van Wimersma Greidanus, Van Ree and De Wied, 1983; Meisenberg and Simmons, 1983). The occurence of vasopressin and oxytocin in neuronal networks in the brain in combination with the fact that these peptides have actions in the CNS, has led to the postulate that in the brain they act as neuromodulators of transmitter systems and, hence, are participating in the regulation of brain function. There is considerable evidence in support of the hypothesis that the central action of vasopressin is, at least in part, mediated by catecholaminergic systems in the brain (Tanaka, De Kloet, De Wied and Versteeg, 1977a; Tanaka, Versteeg and De Wied, 1977b; Versteeg, Tanaka and De Kloet, 1978; Versteeg, De Kloet, Van Wimersma Greidanus and De Wied, 1979; Kovacs, Bohus and Versteeg, 1979a, 1979b; Kovacs, Bohus, Versteeg, De Kloet and De Wied, 1979c; Van Heuven-Nolsen, De Kloet, De Wied and Versteeg, unpublished; Versteeg, 1983). Much less data are available concerning such an interaction of the nonapeptide oxytocin. The only data come from studies in which rather large parts of the brain were examined (Telegdy and Kovacs, 1979a, 1979b; Schwarzberg, Kovacs, Szabo and Telegdy, 1981; Kovacs and Telegdy, 1983). The aim of the present study was to obtain detailed information concerning where in the brain catecholamine metabolism is affected by oxytocin. Therefore, the effect of oxytocin on the disappearance of noradrenaline and dopamine induced by α-methyl-*p*-tyrosine was studied in a selected number of nuclei in the brain. The selection of these nuclei was based on knowledge about the anatomy of the oxytocin-containing systems in the brain (see Buys, 1983) and on the previous reports of the effects of vasopressin and oxytocin on brain function (Tanaka *et al.*, 1977a, b; Versteeg *et al.*, 1978, 1979; Kovacs *et al.*, 1979a, b, c; Van Heuven-Nolsen *et al.*, unpublished; Versteeg, 1983).

METHODS

Male Wistar rats, weighing 140–160 g at the time of the operation, were used. The animals were kept under a controlled light–dark schedule (lights on between 6 a.m. and 8 p.m.) and had access to food and tap water *ad libitum*. Polyethylene cannulae were implanted in the lateral ventricle as described previously (De Wied, 1976). After a recovery period of 5 days, the rats were subjected to the following treatment schedule. An intraperitoneal injection with α-methyl-*p*-tyrosine methylester HCl (α-MPT;

Labkemi AB, Goteborg, Sweden; 300 mg/kg), was followed 30 min later, by the intracerebroventricular injection of 1 μl saline or of oxytocin in doses of 1, 10, 100 and 1000 pmol (which is approx. 1, 10, 100 and 1000 ng, respectively). This dose of α-methyl-*p*-tyrosine was selected because it yields a 95% inhibition of brain tyrosine hydroxylase over a period from 20 min after injection up to 300 min (Moleman and Bruinvels, 1976). Three hours after the intracerebroventricular injection, i.e. 3.5 hr after the injection of α-methyl-*p*-tyrosine, the rats were decapitated. The brains were rapidly taken out of the skull, frozen on dry ice and stored at -80°C. The brains were cut in 300 μm sections in a cryostat at -10°C. Brain nuclei were punched according to the microdissection method described by Palkovits (1980), homogenized in 70 μl 0.1 N $HClO_4$. The homogenate was centrifuged (15 min, 15,000 *g*, 4°C). Noradrenaline and dopamine were assayed radioenzymatically in 20 μl samples of the supernatant as described previously (Van der Gugten, Palkovits, Wijnen and Versteeg, 1976). The pellet was redissolved in 1.1 N NaOH and an aliquot of this solution was used for protein assay (Lowry, Rosebrough, Farr and Randall, 1951). Data were calculated as pg catecholamine per μg protein ± SEM ($n = 5$–8). The data were analyzed by one-way analysis of variance (ANOVA) and Student's *t*-test (two-tailed). A *P* value <0.05 was considered to indicate a significant difference.

RESULTS

The results of the experiments are summarized in Tables 1 and 2. Intracerebroventricular injection of oxytocin, 0.5 hr after treatment with α-methyl-*p*-tyrosine induced changes in the disappearance of noradrenaline in only a restricted number of brain nuclei. A significant decrease in the disappearance of noradrenaline was found in the lateral septum, the medial septum and the anterior hypothalamic area. The opposite effect, namely an increased utilization of noradrenaline was found in the nucleus supraopticus (Table 1). A tendency towards an increase in disappearance of noradrenaline was found in the dorsal septum, whereas in the lateral amygdala in tendency towards a decrease was found (Table 1).

No significant effects were found on the disappearance of dopamine induced by α-methyl-*p*-tyrosine in any of the brain nuclei studied. Tendency towards a decrease in the disappearance of dopamine were observed in the nucleus caudatus, medial septum and globus pallidus.

DISCUSSION

The present results show that the intracerebroventricular administration of oxytocin affects the disappearance of catecholamines induced by α-methyl-*p*-tyrosine in a restricted number of brain nuclei. Significant effects were only found on the

Table 1. Effect of oxytocin on disappearance of noradrenaline induced by α-methyl-*p*-tyrosine in discrete brain nuclei

	Noradrenaline (pg/g protein)				
		Oxytocin (pmol)			
Brain region	Saline	1	10	100	1000
Nucleus accumbens	3.0 ± 0.3	2.3 ± 0.4	3.2 ± 0.5	2.4 ± 0.3	2.6 ± 0.7
Nucleus caudatus	nd	nd	nd	nd	nd
Dorsal septal nucleus	5.0 ± 0.3	5.4 ± 0.7	4.7 ± 0.4	4.3 ± 0.3	3.6 ± 0.4*
Lateral septal nucleus	11.8 ± 0.7	18.2 ± 1.0*	16.7 ± 1.2*	12.8 ± 1.2	13.6 ± 0.8
Medial septal nucleus	4.6 ± 0.4	6.5 ± 0.4*	6.3 ± 0.6*	6.7 ± 1.0	4.7 ± 0.3
Medial preoptic nucleus	18.4 ± 1.9	18.5 ± 1.3	16.3 ± 1.8	16.0 ± 1.4	17.3 ± 3.1
Nucleus interstitialis striae terminalis	28.8 ± 2.9	34.6 ± 5.6	28.0 ± 4.6	29.4 ± 4.6	29.3 ± 3.5
Nucleus supraopticus	19.0 ± 2.8	13.3 ± 1.7	12.0 ± 0.8*	14.0 ± 2.0	21.2 ± 2.5
Nucleus paraventricularis	29.2 ± 3.6	25.0 ± 3.6	28.5 ± 2.5	27.0 ± 4.7	23.3 ± 2.9
Nucleus periventricularis	27.6 ± 2.3	24.0 ± 2.7	26.9 ± 1.2	24.3 ± 1.2	23.3 ± 2.4
Anterior hypothalamic area	8.9 ± 0.9	9.0 ± 1.0	12.1 ± 1.1*	10.4 ± 0.9	7.8 ± 0.9
Globus pallidus	2.6 ± 0.3	3.1 ± 0.4	3.1 ± 0.4	2.9 ± 0.3	3.9 ± 0.4
Nucleus dorsomedialis	29.7 ± 4.3	30.4 ± 3.1	30.0 ± 2.2	29.6 ± 2.1	26.1 ± 3.0
Medial amygdala	2.3 ± 0.3	2.8 ± 0.4	2.3 ± 0.3	1.9 ± 0.2	2.1 ± 0.5
Central amygdala	6.0 ± 0.5	7.2 ± 0.9	7.3 ± 1.3	6.7 ± 0.9	7.8 ± 0.8
Lateral amygdala	3.8 ± 0.6	4.1 ± 0.5	5.7 ± 0.4*	5.2 ± 0.6	5.4 ± 1.2
Basal amygdala	3.3 ± 0.4	3.4 ± 0.5	3.0 ± 0.7	2.7 ± 0.5	3.1 ± 0.4
Gyrus dentatus	1.6 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	1.6 ± 0.1	1.6 ± 0.2
Nucleus parafascicularis	2.4 ± 0.3	2.6 ± 0.2	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.1
Nucleus ruber	2.1 ± 0.3	1.8 ± 0.1	1.9 ± 0.2	1.7 ± 0.1	2.0 ± 0.2
Substantia grisea centralis dorsalis	2.9 ± 0.3	2.7 ± 0.4	2.6 ± 0.3	3.0 ± 0.3	2.0 ± 0.2
Substantia grisea centralis ventralis	4.4 ± 0.7	6.7 ± 1.1	5.7 ± 0.7	6.5 ± 1.7	6.7 ± 1.1
A 8 region	2.5 ± 0.3	3.4 ± 0.4	2.5 ± 0.4	2.3 ± 0.4	2.5 ± 0.2
A 9 region	4.2 ± 0.8	4.0 ± 0.6	3.1 ± 0.6	3.4 ± 0.9	4.7 ± 0.8
A 10 region	10.5 ± 1.1	12.8 ± 1.6	12.7 ± 1.0	12.2 ± 1.0	12.0 ± 1.0
A 6 region	19.3 ± 3.0	21.0 ± 3.9	11.7 ± 1.4	17.7 ± 2.7	20.0 ± 2.5
A 2 region	41.2 ± 7.5	37.3 ± 5.4	44.9 ± 4.9	36.2 ± 4.2	41.9 ± 4.5
Nucleus tractus solitarii (rostralis)	16.0 ± 2.5	10.6 ± 1.0	20.4 ± 3.1	18.7 ± 4.1	19.3 ± 2.3

Analysis of variance for noradrenaline in the dorsal septal nucleus $F(4,34) = 1.54$, for the medial septal nucleus $F(4,35) = 3.00$, $P < 0.05$, for the lateral septal nucleus $F(4.30) = 9.18$, $P < 0.005$, for the nucleus supraopticus $F(4,35) = 2.48$, $P < 0.05$, for the anterior hypothalamic area $F(4,36) = 2.87$, $P < 0.05$ and for the lateral amygdala $F(4,36) = 2.18$. Mean values ± SEM are given ($n = 5$–8). *$P < 0.05$ for difference with saline treated control (Student's *t*-test).

Table 2. Effect of oxytocin on disappearance of dopamine induced by α-methyl-*p*-tyrosine in discrete brain nuclei

	Dopamine (pg/g protein)				
		Oxytocin (pmol)			
Brain region	Saline	1	10	100	1000
Nucleus accumbens	18.0 ± 2.0	21.4 ± 1.2	21.9 ± 2.0	20.0 ± 2.0	20.0 ± 1.6
Nucleus caudatus	16.3 ± 0.9	19.2 ± 2.3	24.0 ± 3.9*	17.1 ± 2.0	17.1 ± 1.3
Dorsal septal nucleus	7.1 ± 0.8	5.9 ± 0.4	6.4 ± 0.6	6.6 ± 1.0	6.4 ± 1.5
Lateral septal nucleus	14.5 ± 2.0	13.6 ± 2.7	20.8 ± 3.3	22.0 ± 5.7	18.1 ± 1.3
Medial septal nucleus	3.2 ± 0.6	5.6 ± 0.6*	4.9 ± 1.0	5.8 ± 1.2	3.7 ± 0.4
Medial preoptic nucleus	4.6 ± 0.5	5.3 ± 1.4	5.6 ± 0.9	4.4 ± 0.7	4.6 ± 1.0
Nucleus interstitialis stria terminalis	6.4 ± 1.8	6.2 ± 1.6	6.2 ± 0.8	7.4 ± 1.4	6.6 ± 1.3
Nucleus supraopticus	10.6 ± 1.3	8.8 ± 1.7	7.6 ± 1.7	11.2 ± 2.8	11.6 ± 3.7
Nucleus paraventricularis	2.1 ± 0.2	1.6 ± 0.2	1.8 ± 0.6	1.6 ± 0.3	1.9 ± 0.2
Nucleus periventricularis	1.9 ± 0.1	2.4 ± 0.3	1.6 ± 0.1	2.0 ± 0.2	1.8 ± 0.1
Anterior hypothalamic area	1.2 ± 0.4	2.3 ± 0.6	1.3 ± 0.4	1.1 ± 0.2	1.5 ± 0.4
Globus pallidus	2.2 ± 0.4	3.8 ± 0.9	3.3 ± 0.5	3.5 ± 0.6	4.8 ± 1.0*
Nucleus dorsomedialis	1.0 ± 0.2	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.1 ± 0.1
Medial amygdala	nd	nd	nd	nd	nd
Central amygdala	3.7 ± 0.9	3.9 ± 0.8	3.2 ± 0.4	4.9 ± 0.9	4.1 ± 0.7
Lateral amygdala	0.7 ± 0.2	1.0 ± 0.2	0.7 ± 0.1	0.8 ± 0.2	1.0 ± 0.3
Basal amygdala	1.2 ± 0.3	1.0 ± 0.2	0.7 ± 0.1	0.7 ± 0.1	0.8 ± 0.1
Gyrus dentatus	nd	nd	nd	nd	nd
Nucleus parafascicularis	nd	nd	nd	nd	nd
Nucleus ruber	nd	nd	nd	nd	nd
Substantia grisea centralis dorsalis	0.8 ± 0.3	0.4 ± 0.1	nd	0.5 ± 0.1	0.5 ± 0.1
Substantia grisea centralis ventralis	nd	nd	nd	nd	nd
A 8 region	1.0 ± 0.2	1.2 ± 0.2	0.8 ± 0.2	1.2 ± 0.3	0.7 ± 0.1
A 9 region	2.8 ± 0.8	2.1 ± 0.6	1.9 ± 0.5	3.1 ± 1.3	3.5 ± 1.3
A 10 region	4.4 ± 0.5	7.1 ± 1.9	5.2 ± 0.8	6.1 ± 0.5	4.3 ± 0.8
A 6 region	0.8 ± 0.1	1.3 ± 0.2	0.9 ± 0.3	1.1 ± 0.2	1.3 ± 0.2
A 2 region	1.3 ± 0.2	1.1 ± 0.3	0.7 ± 0.1	0.8 ± 0.2	1.0 ± 0.2
Nucleus tractus solitarii (rostralis)	nd	nd	nd	nd	nd

Analysis of variance for dopamine in the nucleus caudatus $F(4,38) = 1.88$, for the medial septal nucleus $F(4,34) = 1.58$ and for the globus pallidus $F(4,38) = 1.60$. Mean values ± SEM are given ($n = 5$–8). *$P < 0.05$ for difference with saline treated control (Student's t-test).

disappearance of noradrenaline; no significant effects on utilization of dopamine could be detected. The dose–response curves observed for the effects of oxytocin on utilization of noradrenaline in the medial septal nucleus, lateral septal nucleus, nucleus supraopticus and anterior hypothalamic area are non-linear, bell-shaped, with as the only exception, the dorsal septal nucleus. In this nucleus oxytocin increased utilization of noradrenaline only after the largest dose of oxytocin (1 nmol).

In general, the effects found in the present study were not as widespread as those previously found after administration of vasopressin (Tanaka *et al.*, 1977b). It was found that oxytocin attenuated utilization of noradrenline, whereas previously it was observed that, in general, vasopressin had a stimulatory effect, with as the only exception an attenuating effect in the nucleus supraopticus. In the present study an increased utilization of noradrenaline was found in the nucleus supraopticus after intracerebroventricular treatment with oxytocin. So, again, also in this nucleus the effect of oxytocin was opposite to that seen after vasopressin. Opposite effects of the two neuropeptides have also been reported on behaviour and neuroendocrine regulation, e.g. passive avoidance behaviour (Bohus, Kovacs and De Wied, 1978), self-administration of heroin (Van Ree *et al.*, 1978) brain stimulation reward (Schwarzberg, Hartman, Kovacs and Telegdy, 1976) and the release of ACTH (Legros, Chiodera and Demey-Ponsart, 1982).

Intracerebroventricular treatment of rats with oxytocin (presents results) and vasopressin (Tanaka *et al.*, 1977a) resulted in a stimulatory effect on the utilization of noradrenaline in the dorsal septal nucleus. That in the dorsal septal nucleus, oxytocin has a vasopressin-like effect, also holds for effects on the hippocampal EEG during paradoxal sleep (Urban, 1981) and for the effects on spontaneous and glutamate-induced electrical activity of single neurones (Joëls and Urban, 1982) and passive avoidance behaviour (Kovacs *et al.*, 1979). It is tempting to speculate that in the dorsal septum oxytocin exerts its effects via (putative) vasopressin receptors. Perhaps the recently-discovered receptor system for vasopressin in the dorsal septal area of the brain of the rat (Van Leeuwen and Wolters, 1984; Biegon, Terlou, Voorhuis and De Kloet, 1984) displays some affinity for oxytocin which could explain the fact that oxytocin has similar effects as vasopressin in this brain region in larger concentrations. The fact that a large dose of oxytocin (1 nmol) could act on vasopressin receptors to produce an opposite effect, could explain the observed bell-shaped dose–response curves on utilization of noradrenaline in the other brain nuclei.

An extensive neuronal network containing oxytocin exists in the brain (Buys, 1983). Interestingly, the nuclei where effects were found in the present study contain cell-bodies (nucleus supraopticus) or terminals (other regions) of the central oxytocin-containing system. This makes it likely that endogenous oxytocin also modulates the activity of central

catecholamine-containing neurones. This holds only for the forebrain. In the hindbrain, though strongly innervated with oxytocin-containing fibres, no effects were found on the disappearance of catecholamines induced by α-methyl-*p*-tyrosine. In this respect oxytocin differs from vasopressin, which was found to affect utilization of catecholamines in a number of brainstem nuclei (Tanaka *et al.*, 1977).

Most of the data in the literature concerning the effects of oxytocin on catecholamines in brain came from studies in which rather large parts of the brain were examined. Ten minutes after administration of oxytocin it was found that the concentration of noradrenaline in the septum, hypothalamus and striatum was decreased (Telegdy and Kovacs, 1979a, b). Intracerebroventricular administration of oxytocin was found to result in a decrease in the concentration of dopamine and noradrenaline in the hypothalamus, as well as that of dopamine in the mesencephalon, 4 hr after the injection of the peptide (Schwarzberg *et al.*, 1981). Since changes in concentrations of neurotransmitter are difficult to interpret in terms of increased or decreased neuronal activity, turnover studies are thought to give a better indication of the functional state of a particular neuronal system. Using an identical experimental design as the one performed in the present study, Kovacs and Telegdy (1983) found that the disappearance of noradrenaline was increased in the hypothalamus and disappearance of dopamine in the striatum was increased and decreased in the hypothalamus and mesencephalon. However, when the peptide was injected together with the tyrosine hydroxylase inhibitor, different results were obtained; a decreased disappearance of dopamine and noradrenaline in the striatum and an increase in disappearance of dopamine in the hypothalamus was observed (Telegdy and Kovacs, 1979a, b; Kovacs and Telegdy, 1983). Since, in the present study, a different dissection method has been employed, the results are not directly comparable to the above data. The only parts of the brain that are comparable are the striatum and the nucleus caudatus. However, in the nucleus caudatus, nor in any other brain nucleus, significant differences were found in the present study. Interpretation of the results obtained by Kovacs and Telegdy (1983) for the striatum is complicated by the fact that, with different experimental procedures, opposite results were obtained. The present results do not corroborate those findings. Possible factors contributing to this are the differences in dose level and dissection method.

In conclusion, it can be said that the present data provide evidence for a specific interaction between oxytocin and distinct populations of noradrenaline-containing neurones in the brain of the rat.

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