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7. The animals were observed on a video monitor linked to an infrared-sensitive camera. The camera, together with the infrared light source, was mounted directly over the test area. To aid the animals in locating the objects in the dark, three light-emitting diodes were recessed in the testing board, one 4.5 cm in front of each well. During the sample presentation, only the central diode was lit, whereas during the test part of the trial, both lateral diodes were lit. That the animals could not see the objects under these conditions is indicated by the following: (i) near the end of the light-dimming phase all animals' scores dropped from criterion to chance levels; (ii) the monkeys did not subsequently reattain criterion levels of performance until they were observed on the video monitor to be deliberately comparing the objects by touch; and (iii) neither of two dark-adapted human observers tested in the same situation could detect the presence of the objects visually.
8. The animals were given a tactual memory performance test after they attained the criterion in the dark. In this performance test the delays between sample presentation and choice were increased from 10 seconds to 30, 60, and finally 120 seconds, in blocks of 100 trials each. In this and all other stages of the experiment, the monkeys were trained at the rate of 20 trials per day, 5 or 6 days per week.
9. The animals were retrained first in the dark to obtain a measure of tactile memory uncontaminated by any postoperative visual experience with the objects. After being retrained in each modality, animals were given the performance test described in (*8*) in that modality. By the end of this training, the animals had received an average of about 2000 trials with the same set of objects on the two intramodal tasks. Mean trials for amygdalectomized and hippocampectomized monkeys, respectively: Before surgery—light, 513 and 540; dark, 433 and 413. After surgery—dark, 920 and 427; light, 400 and 400.
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Methionine and Leucine Enkephalin in Rat Neurohypophysis: Different Responses to Osmotic Stimuli and T_2 Toxin

Abstract. *Specific radioimmunoassays were used to measure the effects of hypertonic saline (salt loading), water deprivation, and trichothecene mycotoxin (T_2 toxin) on the content of methionine enkephalin (ME), leucine enkephalin (LE), α-neoendorphin, dynorphin A, dynorphin B, vasopressin, and oxytocin in the rat posterior pituitary. Concentrations of vasopressin and oxytocin decreased in response to both osmotic stimuli and treatment with T_2 toxin, but the decrease was greater with osmotic stimulations. Similarly, concentrations of LE and dynorphin-related peptides declined after salt loading and water deprivation; LE concentrations also decreased after treatment with T_2 toxin. The concentration of ME decreased after water deprivation, did not change after salt loading, and increased after T_2 toxin treatment. The differentiating effects of these stimuli on the content of immunoreactive LE and ME are consistent with the hypothesis that LE and ME may be localized in separate populations of nerve endings with different roles in the posterior pituitary.*

Some investigators have reported that enkephalin-containing peptides inhibit the release of vasopressin and oxytocin from the posterior pituitary (*1*); others have reported that these peptides facilitate their release (*2*). At least two precursors provide enkephalin-containing peptides in the rat brain: proenkephalin A and proenkephalin B (prodynorphin). Proenkephalin A contains four copies of methionine enkephalin (ME) and one copy each of leucine enkephalin (LE), ME-Arg-Phe, and ME-Arg-Gly-Leu (*3*). Some of these peptides in turn are part of longer peptide sequences (for example, peptides I, F, E, and B) (*4*). Proenkephalin B contains three LE sequences, each of which represents the amino terminus of α-neoendorphin, dynorphin A, or dynorphin B (*5*). Different cells seem to process the enkephalin precursors in different ways. For example, chromaffin cells of the adrenal medulla make and store substantial amounts of high molecular weight enkephalin precursors as well as enkephalin octa- and heptapeptides (*4*). In the brain, however, most of the enkephalin measured in radioimmunoassays is present as ME, LE, ME-Arg-Phe, and Me-Arg-Gly-Leu. There is little or no high molecular weight material reacting with antibodies to enkephalin (*4*). In the posterior pituitary there are substantial amounts of ME and LE (*6–8*) but very little or no ME-Arg-Phe and ME-Arg-Gly-Leu (*8*). Thus, the proenkephalin A molecule can give rise to a variety of cellular secretory products in different tissues depending on the extent and pattern of its intracellular processing.

Proenkephalin B–derived peptides are present in high amounts in the posterior pituitary and throughout the brain but in low amounts in the adrenal gland (*9, 10*). Although proenkephalin B contains three LE sequences, it has been argued that LE derives exclusively from the single copy of LE in the proenkephalin A precursor (*4*). This is because the molar ratios of ME to LE in various areas of the brain (~4:1) correspond roughly to the ratio in the proenkephalin A precursor and because the regional distributions of dynorphin and enkephalin (LE or ME) in the brain differ (*11*). However, we have suggested that LE in the rat substantia nigra is derived mainly from proenkephalin B–containing neurons (*12*). To examine the functional relations among LE, ME, and dynorphin in the posterior pituitary, we used specific radioimmunoassays to measure amounts of ME, LE, and dynorphin-related peptides as well as vasopressin and oxytocin in the posterior pituitary of male Sprague-Dawley rats (200 to 250 g in body weight) under conditions of enhanced secretory activity. We found differentiating alterations in concentrations of LE and ME in the neural lobes of rats after hypertonic saline (salt loading) and treatment with

T_2 toxin. These findings imply that LE and ME are contained in distinct opiate inputs to the posterior pituitary and thus may have different physiological roles.

One group of rats was given saline (2 percent NaCl) to drink for 100 hours. A second group was deprived of drinking water for 100 hours. Rats given free access to tap water served as controls for both groups. A third group of rats was injected intravenously (1 mg/kg) with T_2 toxin [3α-hydroxy-4β,15-diacetoxy-8α-(3-methylbutyryloxy)-12,13-epoxytri-Δ^9-chothecene], a trichothecene metabolite of several species of *Fusarium* that produces profound, centrally mediated autonomic changes (*13*). Control rats were injected with vehicle.

After 100 hours of salt loading or water deprivation and 6 to 8 hours after administration of T_2 toxin, rats were killed by decapitation. The posterior lobes of the pituitary glands were isolated under a dissecting microscope and homogenized in 200 μl of 0.1*N* HCl. Portions (20 μl each) of the homogenates were removed for determination of protein content (*14*). The remainder was centrifuged at 2000*g* for 10 minutes at 4°C, and the supernatant was transferred to polypropylene tubes (12 by 75 mm) and dried in a vacuum centrifuge. The radioimmunoassay procedures used have been described, as have the specificities of the antisera used to measure amounts of dynorphin A (1–17) (*15*), dynorphin A (1–8) (*16*), dynorphin B (*17*), α-neoendorphin (*18*), β-neoendorphin (*19*), LE (*15*), ME-Arg-Gly-Leu (*12*), ME-Arg-Phe (*8*), ME (*20*), metorphamide (*21*), oxytocin (*22*), and vasopressin (*23*).

As expected, salt loading and water deprivation resulted in decreased concentrations of both vasopressin and oxytocin in the posterior pituitary and in significantly increased concentrations in plasma (Tables 1 and 2). Six to eight hours after administration of T_2 toxin to rats, concentrations of both vasopressin and oxytocin in the posterior pituitary decreased. Osmotic stimuli augment the synthesis of oxytocin and vasopressin in hypothalamic magnocellular neurons as well as the release of these peptides from the neurohypophysis (*24*), but their concentrations in the posterior pituitary decrease during osmotic stimulation because the rate of their release is greater than the rate of their biosynthesis.

The amounts of dynorphin-related peptides in the neural lobe also declined after salt loading and water deprivation (Table 1) (*25*). Dynorphin has been shown to coexist with vasopressin in magnocellular hypothalamic neurons

Table 1. Concentrations of peptides in the posterior pituitary of rats after 100 hours of salt loading (2 percent saline) or water deprivation and after 6 to 8 hours of treatment with T_2 toxin. Values are expressed as picomoles of peptide per milligram of protein for the opioid peptides and as nanomoles of peptide per milligram of protein for vasopressin and oxytocin (mean ± S.E.M.). When a percentage change is given, the experimental and control group differed significantly (statistical analysis was by *t*-test with Bonferroni correction). N.D., not determined.

Peptide	Osmotic stimuli (*n*)					T_2 toxin treatment (*n*)		
	Control	Salt loading*	Percentage change	Water deprivation†	Percentage change	Control	Toxin	Percentage change
Methionine enkephalin	5.74 ± 0.42 (22)	5.71 ± 0.71 (8)		3.07 ± 0.33 (14)	−46.6	6.13 ± 0.99 (8)	13.3 ± 1.86‡ (7)	+120.7
Leucine enkephalin	12.12 ± 0.72 (19)	2.19 ± 0.21 (9)	−81.9	2.70 ± 0.31 (14)	−77.7	15.44 ± 1.57 (7)	8.24 ± 1.11‡ (7)	−46.6
α-Neoendorphin	24.11 ± 1.35 (22)	7.92 ± 0.82 (10)	−67.1	5.89 ± 0.50 (14)	−75.6	23.57 ± 3.04 (8)	22.53 ± 3.86 (7)	
β-Neoendorphin	22.38 ± 1.12 (22)	4.65 ± 0.51 (10)	−79.6	3.97 ± 0.42 (14)	−82.3	N.D.	N.D.	
Dynorphin A (1–17)	5.65 ± 0.36 (18)	1.39 ± 0.27 (10)	−75.4	2.22 ± 0.40 (10)	−60.7	5.22 ± 0.34 (8)	4.81 ± 0.42 (7)	
Dynorphin A (1–8)	14.38 ± 0.98 (19)	2.70 ± 0.32 (10)	−81.2	2.91 ± 0.39 (13)	−79.7	N.D.	N.D.	
Dynorphin B	24.55 ± 1.84 (19)	3.47 ± 0.52 (10)	−85.9	4.24 ± 0.32 (14)	−82.7	22.13 ± 1.95 (8)	18.80 ± 1.80 (7)	−22.9
Vasopressin	4.52 ± 0.31 (18)	0.48 ± 0.07 (10)	−89.3	0.17 ± 0.07 (12)	−96.3	4.95 ± 0.27 (8)	3.83 ± 0.33§ (7)	−32.2
Oxytocin	4.64 ± 0.24 (20)	1.02 ± 0.13 (10)	−78.2	0.78 ± 0.10 (11)	−83.2	6.67 ± 0.47 (8)	4.52 ± 0.45‡ (7)	

*$P < 0.002$ for all peptides, except ME, compared to control. †$P < 0.002$ compared to control. ‡$P < 0.01$ compared to control. §$P < 0.05$ compared to

(*26*). Dynorphin A (1–8) has been revealed in the same neurosecretory vesicles as vasopressin and vasopressin-associated neurophysin in the neural lobe of the rat by electron microscopic immunocytochemistry (*27*). These results suggest that dynorphin may be released in the neural lobe together with vasopressin during the antidiuretic response (*26*). Thus, the decreased concentrations of dynorphin-related peptides in the posterior pituitary after salt loading or water deprivation may be a result of enhanced secretion analogous to decreases in vasopressin and oxytocin. That dynorphin concentrations in the supraoptic nucleus of rats increase after administration of 2 percent saline (*28*) suggests that the increased rate of dynorphin release that we propose may be accompanied by a compensatory increase in its biosynthesis (*29*).

The concentration of LE was decreased in the posterior pituitary after salt loading (2 percent saline) or water deprivation (Table 1). The magnitude of the depletion of LE from the neural lobe was similar to that of the dynorphin-related peptides. Again, the depletion of LE from the posterior pituitary after osmotic stimuli may result from an increase in its release from the gland.

Methionine enkephalin was depleted from the posterior pituitary after water deprivation to a lesser extent than LE and the dynorphin-related peptides. However, there was no change in the concentration of ME in the posterior pituitary after salt loading, and there was an increase after treatment with T_2 toxin (Table 1). There are several possible explanations for these findings. ME may be sequestered in larger precursor peptides in well-hydrated rats, and these peptides may be cleaved to generate ME on demand. However, we were unable to detect significant amounts of ME-Arg-Gly-Leu, ME-Arg-Phe, or metorphamide in rat posterior lobe extracts [less than 0.04, 0.085, and 0.04 pmol per milligram of protein, respectively (n = 5 per group)]. This lack of proenkephalin A–related peptides suggests (i) that proenkephalin A may be processed completely to ME in posterior pituitary nerve endings or (ii) that the ME arises from a precursor other than proenkephalin A. While ME could derive from proopiomelanocortin, no processing of this peptide to ME has been shown in studies of adrenocorticotropic hormone and β-endorphin biosynthesis. Thus, the existence of another uncharacterized precursor for ME must be considered. Coexistence of ME with oxytocin in most but not all oxytocin-positive neurosecretory

Table 2. Concentrations (femtomoles per milliliter) of vasopressin and oxytocin in plasma from rats after 100 hours of salt loading (2 percent saline) and water deprivation. Values are means ± S.E.M. Statistical analysis was by *t*-test with Bonferroni correction. $n = 5$ animals per group.

Peptide	Treatment		
	Control	Salt loading*	Water deprivation
Vasopressin	1.78 ± 0.22	3.99 ± 0.17	3.19 ± 0.36†
Oxytocin	2.18 ± 0.41	9.58 ± 1.07	8.25 ± 1.61‡

*$P < 0.002$ compared to control. †$P < 0.05$ compared to control. ‡$P < 0.02$ compared to control.

granules of the posterior pituitary has been shown by electron microscopy (*30*). Thus, ME and oxytocin would be expected to respond similarly under the same physiological stimuli. This does not occur with salt loading or treatment with T_2 toxin, suggesting possible involvement of separate populations of termini containing ME and oxytocin.

Quantitative comparison of the concentrations of ME and LE in the posterior pituitary revealed a molar excess of LE over ME, giving a molar ratio different from that predicted if all the LE and ME were derived from the proenkephalin A precursor and if this precursor were processed completely to the small enkephalin peptides. Other studies have shown that the molar ratio of ME to LE in the rat posterior pituitary is 1:1 (*6*) or 3:1 (*7*) and in the neurointermediate lobe is 6:1 (*8*). The separation of the intermediate lobe from the posterior pituitary is critical because the intermediate lobe contains a molar excess of ME over LE [6.60 ± 0.88 pmol of ME per milligram of protein ($n = 6$) compared to 2.65 ± 0.85 pmol of LE per milligram of protein ($n = 6$); mean ± standard error of the mean (S.E.M.)]. Early studies measuring enkephalins in the posterior pituitary were carried out before the discovery of the dynorphin-related peptides, and the specificity of the LE antisera used in these studies is not clear. The preponderance of LE over ME in the posterior pituitary may result from preferential liberation of LE from proenkephalin A while ME remains part of larger peptides. As discussed above, however, there is no evidence that such ME-containing peptides are present in the posterior pituitary. Other explanations, such as preferential release or degradation of ME versus LE, are conceivable but unlikely. The simplest explanation for the excess of LE is that the LE in the neural lobe comes mainly from proenkephalin B, which contains three LE sequences. We have suggested that, in the substantia nigra, proenkephalin B may serve as a major source of LE (*12*).

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