

This Week's Citation Classic®

de Wied D. The influence of the posterior and intermediate lobe of the pituitary and pituitary peptide on the maintenance of a conditioned avoidance response.

Int. J. Neuropharmacol. 4:157-67, 1965.

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Removal of the posterior/intermediate lobe of the pituitary facilitated extinction of shuttle-box avoidance behavior. This abnormal behavior could be restored by administration of peptide hormones related to vasopressin and ACTH. This behavioral effect suggested an important central action of these peptides. [The *SCI*® indicates that this paper has been cited in over 210 publications.]

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The *Classic* paper was the second in a series on the influence of the pituitary gland and pituitary hormones on acquisition and extinction of shuttle-box avoidance behavior. The first, which appeared in 1964 in the *American Journal of Physiology*,¹ dealt with the adenohypophysis and the effect of ACTH and related peptides. Avoidance learning was reduced in adenohypophysectomized rats, which could be amended by treatment with ACTH. The exciting finding was that this effect was not mediated by the adrenal cortex since peptides related to ACTH (α -MSH) (which had nearly no corticotrophic effects) also restored avoidance learning of adenohypophysectomized rats, indicating an extratarget effect possibly directed toward the central nervous system. The experiments reported in the 1965 paper (the *Classic*) were performed before I had done those published in 1964. I had wished to publish them back-to-back in the *Journal of Pharmacology and Experimental Therapeutics*, but the editor insisted that I combine the two papers into one. I refused.

The impetus for the studies was the observation that Smelik² made, and I subsequently confirmed,³ when we were working in the Department of Pharmacology of the Medical Faculty of the University of Groningen, The Netherlands, that removal of the posterior/intermediate lobe of the pituitary resulted in a reduced pituitary-adrenal activation in response to emotional but not systemic stress. It was reasoned

that vasopressin might be involved in the release of ACTH in response to emotional stress. However, I felt that the impaired pituitary response to emotional stress in posterior lobectomized rats could also reflect a behavioral incompetence of these animals to respond to emotional stress. I decided to study the behavior of these rats using avoidance behavior, which is associated with stress and emotion.

Although I had medical training, I spent a year (1957-1958) in Pittsburgh, Pennsylvania, in the Department of Clinical Science with I. Arthur Mirsky, who insisted that I get training from his associate, Robert E. Miller, in some basic techniques and concepts in experimental psychology. They already had studied the influence of ACTH on behavior in monkeys and rats. In fact, we investigated the effect of a synthetic corticosteroid derivative, prednisolone, on extinction of shuttle-box avoidance behavior.

I found that extinction of shuttle-box avoidance behavior was markedly facilitated in posterior lobectomized rats. This could be corrected by chronic treatment with vasopressin, ACTH, or α -MSH. Although these studies on the pituitary gland and on behavior were both done at the end of the 1950s and the beginning of the 1960s, I could not get myself to publish them because I had not mastered enough professional vocabulary to describe the behavioral studies. It took a number of years before I decided to write them up.

I was appointed professor and head of the Department of Pharmacology in the Medical Faculty of the University of Utrecht in 1963. Based on the intriguing results of the pituitary hormones ACTH/MSH and vasopressin, I then decided that the central nervous effect of pituitary and brain peptide hormones should be the main topic of a multidisciplinary research group in the Department of Pharmacology, which, since 1968, has been known as the Rudolf Magnus Institute for Pharmacology. (At that time, the system in The Netherlands allowed for maximal freedom in spending research money, which came as a lump sum via the government to the university and faculty. I don't think that the proposed research would have satisfied peer review evaluation today.) We coined the term "neuropeptide" for these compounds because of their central nervous system effects.⁴ ACTH/MSH and related peptides were found to facilitate learning processes by affecting motivation, concentration, and attention,⁵ and vasopressin and related peptides, to facilitate memory processes.⁶ Evidence was found in later years for neuroleptic-like (γ -type endorphins) and psychostimulant (α -type endorphins) and other effects of peptides derived from β -endorphin.⁵

1. de Wied D. Influence of anterior pituitary on avoidance learning and escape behavior. *Amer. J. Physiol.* 207:255-9, 1964. (Cited 120 times.)
2. Smelik P G. Mechanism of hypophysial response to psychic stress. *Acta Endocrinol.* 33:437-43, 1960.
3. de Wied D. The significance of the antidiuretic hormone in the release mechanism of corticotropin. *Endocrinology* 68:956-70, 1961. (Cited 70 times.)
4. de Wied D, van Wimersma Greidanus T B & Bohus B. Pituitary peptides and behavior: influence on motivational, learning and memory processes. (Boissier J R, Hippus H & Pichot P, eds.) *Neuropsychopharmacology: proceedings of the IX Congress of the Collegium Internationale Neuropsychopharmacologicum*, 7-12 July 1974, Paris, France. Amsterdam: Excerpta Medica, 1975. p. 653-8.
5. de Wied D & Jolles J. Neuropeptides derived from pro-opiomelanocortin: behavioral, physiological, and neurochemical effects. *Physiol. Rev.* 62:976-1059, 1982. (Cited 85 times.)
6. de Wied D. Neurohypophysial hormone influences on learning and memory processes. (Lynch G, McCaugh J L & Weinberger N M, eds.) *Neurobiology of learning and memory*. New York: Guilford Press, 1984. p. 289-312.