SEIZURE DISORDERS

MECHANISM OF ANTICONVULSANT ACTION OF ACTH

The hypothesis that systemic or intraventricular administration of corticotropin (ACTH) acts directly on limbic neurons to modulate corticotropin-releasing hormone (CRH) gene expression, independently of adrenal stimulation, was tested and confirmed in experiments on developing rats (9-11 days postnatal) at the University of California, Irvine. This down-regulation of CRH gene expression was not abolished in adrenalectomized animals, and was prevented by selective blocking of melanocortin receptors. It was reproduced by an ACTH fragment that does not promote the release of steroids. The authors conclude that ACTH activates melanocortin receptors to modulate CRH gene expression in amygdala neurons, supporting a direct, steroid independent anticonvulsant action of ACTH. (Brunson KL, Khan N, Eghbal-Ahmadi M, Baram TZ. Corticotropin (ACTH) acts directly on amygdala neurons to down-regulate corticotropin-releasing hormone gene expression. Ann Neurol March 2001;49:304-312). (Respond: Dr Baram, Departments of Pediatrics and Anatomy/Neurobiology, ZOT 4475, University of California at Irvine, CA 92697).

COMMENT. A direct, steroid independent mechanism of ACTH was postulated following clinical and laboratory animal studies in the 1950s and 60s, in Chicago at the Division of Neurology, Children's Memorial Hospital, and at the University of Utah. Effects of ACTH on seizure thresholds varied with age, and were demonstrated in both intact and adrenalectomized animals (Woodbury,Timiras and Goodman, 1954, 1963; Millichap, Wasserman and Belton, 1957, 1965). Immature rats from birth to 8 days had a high seizure threshold. Between 8 and 16 days, brain excitability increased rapidly, and the threshold to experimental seizures was lowest at 25 to 30 days. Brunson and associates chose immature rats of 9-11 days for their experiments, at a time of relatively low seizure threshold, and equivalent to the age of infants with infantile spasms. ACTH may decrease this age-related excessive brain excitability by repressing CRH expression. Snead OC in an editorial describes this model of research as bedside-to-bench, and back (Ann Neurol 2001;49:288-9).

MORTALITY IN ANTIEPILEPTIC DRUG TRIALS

The incidence and causes of mortality in patients with epilepsy enrolled in antiepileptic drug (AED) trials, and the risk factors for sudden unexplained death in epilespy (SUDEP) were examined in pooled data from New Drug Applications (NDA), at the Center for Drug Evaluation and Research, US FDA, Rockville, MD. Ages ranged from 1 to 72 years, with 10% between 1 and 14 years and 50% between 15 and 34 years. In children, the all-cause mortality rate (ALL) was 4.1 per 1000 person years; and the SUDEP rate was 2.4/1000 person years. Mortality rates increased with increasing age, reaching an ALL of 32 in 55-72 year olds. Sixty-five percent of all deaths were related to the underlying epilepsy. Of risk factors, only age was associated with the incidence of SUDEP, and disease severity is the probable determining factor. Length of epilepsy history, gender, and number of concomitant drugs did not influence the SUDEP rate. (Racoosin JA, Feeney J, Burkhart G, Boehm G. Mortality in antiepileptic drug development programs. Neurology February (2 of 2) 2001;56:514-519). (Reprints: Dr Judith A Racoosin, 5600 Fishers Lane, HFD-120, Rockville, MD 20857).

COMMENT. See Walczak TS et al (Neurology 2001;56:519-525) for SUDEP study.