Pharmacology

UNIQUE EFFECTS OF A PYRROLOPYRIMIDINE (B.W. 58-271) ON THE ELECTRICAL ACTIVITY OF THE BRAIN. Stata Norton. The Wellcome Research Laboratories, Tuckahoe, New York.

B.W. 58-271 (2-methyl 4-benzylamino pyrrolo-[2,3-d] pyrimidine) is an anesthetic in cats, dogs, mice, rats, rabbits, pigeons and man but has certain marked pharmacological differences from ether and pentobarbital. In cats unconsciousness occurred with intravenous doses of 3-4 mg/kg. Doses of 8-16 mg/kg eliminated spontaneous electrical activity of the brain as recorded with macroelectrodes. However, in this "flat brain" various modes of peripheral sensory stimuli resulted in bursts (2-3 sec.) of slow waves in the brain. In order of descending effectiveness in eliciting these bursts were sight, sound, touch and sciatic stimulation. These effects were observed for up to 5 hours without cardiovascular deterioration. Because of the unusual ease with which the EEG was blocked by this compound, recordings of the firing of cortical neurons were made with microelectrodes. Neurons in the postsigmoid and lateral gyri were studied. Block of spontaneous firing paralleled block of spontaneous electrical activity of the EEG. Evoked firing of neurons of the lateral gyrus in response to light and movement across the visual field was independent of effects on the EEG.

Pharmacology

TREMORINE TREMOR IN CHRONIC SPINAL RATS. R.K. Chalmers* and G.K.W. Yim*. Purdue Univ. School of Pharm., Lafayette, Ind.

There have been conflicting reports of Tremorine's ability to induce tremor below the level of section in chronic spinal cats. In this study female Wistar albino rats weighing about 200 gm. were prepared by spinal cordectomy at level T_6-T_9 and challenged with Tremorine (i.p.) during successive stages of spinal shock recovery. All rats showed sustained head and forelimb tremor. As ipsilateral flexion response to toe pinch returned (1 day), Tremorine (up to 20 mg/Kg) induced no spinal tremor. After recovery of the crossed extensor reflex (5 days-7 weeks postop), Tremorine (5-10 mg/Kg) induced periodic tremor bursts and bilateral hind leg and hip movements. Kemadrin (10 mg/Kg) blocked tremors both above and below level of section. Preliminary studies indicated that unilateral section of dorsal roots to hind limb innervation abolished tremor in the ipsilateral leg. Eserine salicylate (1 mg/Kg) and arecoline HBr (5-10 mg/Kg) each produced a similar spinal tremor that was blocked by Kemadrin. In contrast, the quaternary anticholinesterase, prostigmine methylsulfate (0.1-1 mg/Kg) produced a slow quivering tremor of all extremities that was not abolished by Kemadrin or acute limb denervation, indicating action at the myoneural junction. Spinal Tremorine tremors were blocked by acute limb denervation. It is concluded that Tremorine produces definite tremors below the level of section in chronic spinal rats.

Pharmacology

EMETIC AND PYROGENIC EFFECTS OF STAPH. ENTEROTOXIN (S.E.) IN CATS. W.G. Clark*#, G.F. Vanderhooft* and H.L. Borison. Dept. of Pharmacology, Univ. of Utah Med. Coll., Salt Lake City.

Cats were prepared chronically with a retroperitoneal thermocouple and a jugular catheter or a lateral ventricular cannula. Body temp. was recorded automatically at 20 min. intervals. We used purified S.E. (90%) obtained from M.S. Bergdoll (see Arch. Biochem. Biophys., 1959, 85, 62). Emesis was produced regularly by S.E., 1 µg/kg i.v., within 1 hr. With increasing dosage the latency of the emetic response decreased to as little as 7 min. after 4 µg/kg. S.E. in doses of 5 and 10 µg/kg was still effective in eliciting emesis in 3 cats with chronic ablation of the medullary emetic chemoreceptor trigger zone. Lateral ventricular injection of S.E. (17 tests), however, never caused vomiting, even in doses ranging from 1-16 µg in 0.25-1.0 ml of sol. Intravenous S.E., 1 µg/kg, produced marked increases in body temp. in 5 cats with onset occurring before 3 hrs. and peak (at least 3° F) about 9-10 hrs. The fever persisted approximately 24 hrs. Lateral ventricular injection of S.E. also evoked fever, but interpretation of this result remains uncertain. Five cats with chronic midbrain transection continued to show a pyrogenic response but not an emetic response to i.v. S.E. (Supported by USPHS Grant B-491.) #NIH Predoct. Fellow GF-9177.

Pharmacology

LOWERED CONVULSIVE THRESHOLDS TO HEXAFLUORODIETHYL ETHER PRODUCED BY DRUGS WITH DIFFERENTIAL EFFECTS ON BRAIN SEROTONIN AND NOREPINEPHRINE LEVELS. Edward B. Truitt,Jr. and Ethel M. Ebersberger*, Dept.of Pharmacology, Univ.of Maryland Sch.of Med., Baltimore,Md.

Reserpine lowers convulsive thresholds to electroshock, pentylenetetrazol and hexafluorodiethyl ether (HFE). The possibility that this effect might be related to changes in brain levels of Serotonin or Norepinephrine has been investigated by means of three drugs reported to produce a differential change in these amines. Dimethylaminobenzoyl methylreserpate (SU-5171), α-methyl-m-tyrosine(MK345) and α-methyl-3,4-dihydroxy-dl-phenylalanine(α-methyl-DOPA,MK-350) were tested at varying intervals for their action on HFE convulsive thresholds in mice. As previously found for reserpine, the greatest effect was a shorter latency of preconvulsive myoclonic jerks. Clonic convulsive thresholds were not significantly changed, but the frequency of severe tonic convulsions and deaths increased. By comparison to the reported time curves of the action of these three drugs on brain amine levels, the changes in convulsive thresholds seem temporally related to the Serotonin changes in brain. Supported by grant MY-2540

Pharmacology

ALTERATIONS IN RESPONSIVENESS TO RESERPINE FOLLOWING CHRONIC BRAIN LESIONS IN RATS. Martin W. Adler*. Dept. of Pharmacology, Albert Einstein Coll. of Med., New York,N.Y.

An increased sensitivity to the stimulant effects of amphetamine on spontaneous locomotor activity in rats subjected to bilateral lesions of the frontal or posterior cortex was reported in a previous communication (Adler, Fed.Proc. 19:269, 1960). It was also reported that rats with bilateral lesions of the rostral portions of the caudate nucleus did not manifest this change. Utilizing the same indicator, these animals were tested for responsiveness to the depressant effects of reserpine. It has been reported (Smith, et al, J.Pharmacol. Exp.Ther. 117:136, 1956) that in monkeys with frontal, temporal, or combined fronto-temporal lesions, there is a decreased effect of reserpine on an avoidance test in the pooled operated group. In the present study, a dose of 0.5 mg/kg I.P. resulted in a significant decrease in spontaneous locomotor activity in control animals and in animals subjected to the frontal ablations. This was not noted in animals with caudate or posterior lesions. Although the difference between the caudate and the control group was just shy of significance with a multiple range test, the posterior group differed significantly from the control group. (Supported by U.S.P.H.S. Pharmacology Training Grant 2G-65 and Interdisciplinary Grant 2M-6418, National Institute of Mental Health).

Pharmacology

CNS STIMULANTS AND ELECTRICAL BRAIN ACTIVITY IN SPONTANEOUSLY BEHAVING CATS. Barbara B. Brown, Riker Labs., Northridge, Cal.

Effects of LSD, amphetamine and deanol on spontaneous and evoked brain electrical activity and spontaneous behavior were evaluated in "chronic" cats. Behavior changes were subtle; responses indicated alterations in perception and meaning to internal and external stimuli. The cats' behavioral contributions to drug effect were seen both overtly and electrically; amphetamine "calming" hyperactive but alerting lethargic cats, change in space discrimination by LSD; also individual shifts between EEG frequency and behavioral state. LSD (0.0015 mg/kg i.v.) caused frequent rhythmic bursts in cortex, altered hippocampal theta activity, dissociation between cortex and subcortex in alerting response, displacement of EEG dominant frequency with respect to behavioral state. Auditory potentials were reduced, but rhinencephalic and visual potentials were enhanced. Except for photic responses, effects of intraventricular LSD were opposite in direction. d-Amphetamine (0.02 mcg/kg i.v.) caused dissociation between EEG and behavioral states, depressed reticular conduction but enhanced responses to amygdala and photic stimulation. Deanol (10 mg/kg i.v.) shifted relationship between EEG frequency and behavioral state without obvious change in behavior, and enhanced reticular and cortical activity as evaluated by evoked potentials (USPH Grant MY-2855).