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PHARMACOLOGIC ANALYSIS OF THE DEPRESSANT EFFECT OF NICOTINE ON DECEREBRATE RIGIDITY IN THE CAT. K. H. Ginzel and Nancy C. Berry.*Riker Laboratories, Los Angeles, California, 91324

Nicotine depresses γ-efferent discharge and relieves decerebrate rigidity of the γ-type by a reflex action (Ginzel and Eldred, Proc. West. Pharmac. Soc., 1969). Although γ-depression suggests itself as the underlying mechanism, nicotine may conceivably reduce the rigidity also through activation of the Renshaw system known to inhibit the α-motoneuron. In decerebrate preparations and intact cats under chloralose-urethane anesthesia, tension and EMG activity of the quadriceps femoris muscle were recorded. The knee jerk was elicited every 10 sec; its reduction by nicotine reflects the degree of Renshaw inhibition produced by the drug. Nicotine-induced knee jerk inhibition, on the one hand, and nicotine-induced rigidity and EMG depression, on the other, could be differentially affected as follows: Centrally acting dihydro-β-erythroidine which blocks the nicotinic synapse at the Renshaw cell, abolished the former but not the latter; peripherally acting hexamethonium (C_6) which antagonizes the γ-depressant effect of nicotine, blocked the latter but not the former. Neostigmine, for reasons yet to be understood, produced effects similar to those of C_6. These findings suggest that the main factor in the relief of rigidity by nicotine is, indeed, depression of γ-activity.

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BLOCKADE OF BULBOSPINAL INHIBITION BY ANTAGONISTS OF 5-HYDROXYTRYPTAMINE (5-HT). Edmund G. Anderson and B. V. Clineschmidt*. Univ. of Illinois Coll. of Med., Chicago, Ill. 60612.

Most spinal cord 5-HT is associated with nerve terminals of supraspinal origin. The somata of the descending 5-HT neurons largely lie in the brain stem raphe. Since agents elevating cord 5-HT levels alter motor reflexes, we examined the effects of raphe stimulation on segmentally evoked reflexes in the decerebrate cat. The monosynaptic reflex (MSR) evoked by dorsal root or peripheral nerve stimulation could be facilitated or inhibited by antecedent stimulation of various areas in the raphe magnus and obscurus nuclei. Facilitatory responses were unaffected by 5-HT antagonists. LSD (250 μg/kg) immediately blocked inhibition of the MSR by raphe stimulation, often converting it to facilitation. LSD blocked raphe inhibition of MSR's evoked from flexor or extensor nerves, and lasted about 2 hours. Methysergide (0.5 mg/kg) and cinanserin (4 mg/kg) also blocked raphe inhibition. BOL (1 mg/kg) produced a transient (10-15 minute) blockade. Inhibition of the MSR evoked by stimulation of ventral medial reticular formation was also blocked by the 5-HT antagonists. These results suggest 5-HT has a functional role in bulbospinal inhibitory pathways. (Supported in part by USPHS grants NB 05611 and NB 5262.)

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EFFECTS OF 5,5-DIPHENYL-2-THIOHYDANTOIN (DPTH) IN CAT SPINAL CORD. Raines,A., Sohn, Y.J.* & Levitt,B. Dept. Pharmacol. Cornell U. Med Coll New York, N.Y. 10021

DPTH & diphenylhydantoin (DPH) exhibit similar anti-arrhythmic & anticonvulsant properties; both drugs produce ataxia & tremor in large doses. In spinal cats, 20-50 mg DPTH/kg:

a) reduces presynaptic inhibition of gastrocnemius-soleus monosynaptic (2N) pathway. Inhibition was produced by 7 conditioning volleys applied at 250 Hz to posterior biceps & semitendinosus nerves. Conditioning train-test intervals were varied from 50-800 msec. Interestingly, dorsal root potentials, which signal presynaptic depolarization of afferent nerve endings, are augmented and prolonged.

b) produces some depression of posttetanic potentiation of 2N reflex; effects on posttetanic hyperpolarization are unimpressive.

c) produces little effect on 2N spike amplitude but enhances polysynaptic discharges.

Larger doses produce spontaneous discharges in dorsal & ventral roots. The effects described above develop within 10-15 min. These data indicate that DPTH shares properties with both DPH & strychnine. Supported by USPHS 2-T01-GM-00099 & a grant-in-aid from the N.Y. Heart Ass'n.

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PHARMACOLOGICAL INVESTIGATION OF TRANSMISSION AND PRESYNAPTIC INHIBITION OF THE CELLS OF THE DORSAL SPINOCEREBELLAR TRACT OF THE CAT. W. Schlosser* and E. Zavatsky* (Spon: E. B. Sigg) Hoffmann-La Roche Inc., Nutley, N.J. 07110.

Inhibition of the mass discharges of the cells of the dorsal spinocerebellar tract (DSCT) has been shown to be of presynaptic type (J.C.Eccles et al. J. Neurophysiol. 26: 635, 1963). It was, therefore, of interest to see if drugs known to have an action on indirect inhibition of the motoneurone had a similar effect at ascending spinal levels. Recordings of the mass discharges from the dissected Flechsig's fasciculus were made in unanesthetized spinal cats. Appropriate muscle and cutaneous nerves were used to evoke the test and conditioning volleys. The action of i.v. administration of two stimulants (strychnine, 0.1 - 0.2 mg/kg; picrotoxin, 1-4 mg/kg) and two depressants (phenobarbital, 10-80 mg/kg; diazepam, 0.5 - 1.5 mg/kg) were studied. The monosynaptic spike was resistant to all test compounds except phenobarbital which depressed it at high concentrations. Polysynaptic transmission was facilitated by strychnine and depressed by larger doses of phenobarbital. Presynaptic inhibition was enhanced by strychnine and diazepam, and depressed by picrotoxin and phenobarbital. The pharmacology of the cells of the DSCT appears to be similar to that of the motoneurone in many respects.

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THE EFFECTS OF GAMMA BUTYROLACTONE (GBL) AND 1,4-BUTANEDIOL (BD) ON SPINAL SYNAPTIC ACTIVITY. James A. Bell* and Edmund G. Anderson, Dept. of Pharmacology, Univ. of Ill. Coll. of Med., Chicago, Ill.

In acute spinal cats GBL and BD produced dose dependent depression of potentials evoked by supramaximal dorsal root stimulation and recorded from the ventral root and adjacent dorsal root. Depression of the monosynaptic reflex began 1-2 minutes following an I.V. injection of GBL or BD in a dose range of 50-150 mg/kg. Peak depression of all potentials occurred within 40-50 minutes. GBL or BD 100 mg/kg produced complete depression of the monosynaptic reflex while the polysynaptic and dorsal root reflexes were depressed to approximately 40% of control value. All reflexes recovered within 3.5 hrs. of injection.

The I.V. injection of gamma hydroxy butyric acid (GHB) (50-100 mg/kg) also suppressed the monosynaptic reflex to a greater degree than the polysynaptic reflex or the dorsal root reflex. The onset of action of GHB was immediate but maximal effects required 20-30 minutes to develope. GBL and BD are converted in vivo to GHB. Therefore GBL and BD may be acting through GHB which shows an action similar to gamma amino butyric acid on spinal cord receptors (Supported by USPH grant NB 05611).

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SPINAL CORD BLOOD FLOW MEASURED WITH RADIOACTIVE XENON AND THE EFFECTS OF SUCCINYLCHOLINE, GALLAMINE AND CURARE. J.Usubiaga, F.Gollan* Z.Yannakakis* and A. Johnson* Univ.Miami Sch.Med.and VA Hosp. Miami, Fla.

To measure spinal cord blood flow(SCBF), 20 Greyhound dogs had a segment of the cervical, thoracic or lumbar SC exposed under chloralose anesthesia. Intracordal injections of Xe 133 dissolved in methylene blue were made and the washout rate of radioactivity recorded. Postmortem sections of the cord allowed to visualize the spread of the dye. SCBF(White matter) varied from 6 to 15ml/100gr/min. at normotension, normocarbia and normothermia. Injections at the same spot gave reproducible results. Simultaneous measurements at different cord levels gave a ± 10% variation. SCBF(Grey matter) varied from 30 to 69ml/100 gr/min., the highest flows at the anterior horn. These values are lower than those found by Landau(Trans.Am.Neurol.Assoc. 80:125, 1955)using autoradiograms in the cat. Since paralyzing doses of Succinylcholine(2mg/kg), Curare(0.5mg/kg) and Gallamine(3mg/kg) did not modify SCBF, skeletal muscle relaxants can be used satisfactorily during SCBF determinations. (Supported by VA Dept.of Research Grant and USPHS Tr.Grant 6669)