Blood pressure was recorded on a smoked rotating drum through a mercury manometer from the left carotid artery. Drugs were injected in a constant volume of 0.2 ml, through a femoral vein. In all experiments atropine sulphate was injected at a dose of 1 mg/kg i.m. 45 min before administration of oxotremorine. At least 6 experiments were performed in each set.

Results. Administration of oxotremorine sesquifumarate (Aldrich) at doses between 0.5 to 2 µg/kg i.v. resulted in instantaneous and transient fall of blood pressure (Figure a). The vasodepressor effect of oxotremorine was abolished after atropine (Figure a). However, a 100-fold increase in dose of oxotremorine (50 to 200 µg/kg, i.v.) in atropinized rats resulted in a fast increase of blood pressure (Figure a). The vasopressor effect in atropinized rats lasted for 20 to 35 min followed by no subsequent vasodepression. The average percentage of pressor response of oxotremorine after a dose of 100 µg/kg i.v. was found to be 104 ± 12.4 (S.E.). Repeated administration of a vasopressor dose of oxotremorine resulted in complete trachyphylaxis.

The vasopressor effect of oxotremorine in atropinized rats was abolished when repeated 1 h after dibenzyline (1 mg/kg, i.m.) administration. The pressor response to oxotremorine after administration of atropine was absent in reserpinized (1 mg/kg/24 h, i.m. for 48 h) rats (Figure b). Reserpinization was ensured by abolition or marked reduction of i.v. administered tyramine (0.5 mg/kg).

Tetraethylammonium bromide (50 mg/kg, i.v.) similarly reduced the vasopressor response to oxotremorine. Bilateral adrenalectomy either markedly reduced or abolished the pressor response to oxotremorine in atropinized rats (Figure c).

In order to detect any central component in the pressor action of oxotremorine, its effect was investigated in pithed rats before and after atropine. The pressor effect to oxotremorine after atropine could not be demonstrated in pithed rats. However, the vasodepressor effect of low doses of oxotremorine before atropine remained unaltered in pithed rats (Figure d).

Discussion. The results obtained suggest that the pressor response to oxotremorine after cholinergic blockade by atropine is due to ganglionic stimulation and subsequent liberation of catecholamine from the suprarenal medulla. Abolition of pressor responses to oxotremorine by a) the adrenolytic agent dibenzyline; b) the ganglion blocking agent tetraethylammonium; c) bilateral adrenalectomy and d) reserpinization, provide validity for such conclusion. Pressor effect to oxotremorine could not be demonstrated in pithed atropinized rats which indicates that oxotremorine has no effect at peripheral nicotinic site like acetylcholine. However, the peripheral muscarinic action of oxotremorine remained unaltered in pithed rats. Absence of vasopressor response in atropinized pithed rat suggests that liberation of catecholamine from suprarenal medulla is entirely central y mediated. Nicotine has been shown to cause liberation of catecholamine from adrenal medulla through a central mechanism[5]. We, therefore, propose to qualify the pressor response to oxotremorine in atropinized rats as central nicotinic effect of the drug. A stimulant action on the superior cervical ganglion has been reported following close arterial injection of oxotremorine[6] but this may be blocked by atropine and appears to be analogous to the specific effects of other muscarinic agents on autonomic ganglia[7].

Zusammenfassung. Eine zentrale, nikotinartige Wirkung von Oxotremorin wird am Blutdruck der Ratte beschreiben.

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[5] M. Vogt, Pharmac. Rev. *11*, 483 (1959).
[6] W. C. DeGroat and R. L. Volle, Life Sci. *2*, 618 (1963).
[7] A. J. Pappano and R. L. Volle, Life Sci. *1*, 677 (1962).

Effects of Tybamate and Pentylenetetrazol on Spinal Interneurons

It has recently been shown that the central muscle relaxant tybamate (Solacen) acts primarily by depressing spinal polysynaptic reflexes[1,2]. This effect can be adequately explained as a depressant action on spinal internuncial neuronal activity[2]. Similar studies with the analeptic pentylenetetrazol (Metrazol) indicate opposite results, that is, an enhancement of polysynaptic activity with a depression of the electrically evoked monosynaptic response[3,4]. Later reports, attempting to explain these effects by recording the activity of single Renshaw cells following pentylenetetrazol administration, were negative[5]. Also, it appears that pentylenetetrazol does not directly affect motoneuron excitability[6]. With this in mind, the present study was designed to determine whether pentylenetetrazol affected spinal internuncial neuronal activity and also if pentylenetetrazol antagonized the depressant effects of tybamate.

Materials and methods. The experimental procedures employed in this investigation have been previously described[1,2]. Briefly, midcollicular decerebrate cats were prepared under ether anesthesia. Arterial blood pressure was measured from the left common carotid artery and drug injection was via the radial vein. The contralateral polysynaptic extensor reflex was elicited by stimulating the central end of the cut left sciatic nerve and recording contractions of the contralateral quadriceps femoris. For the spinal interneuron studies, decerebration was followed by laminectomy at L_{1-2} and transection of the spinal cord. The animals were artificially ventilated with room air. The dorsal and ventral roots of L_7 were dissected free, sectioned and mounted on Palmer bipolar electrodes for orthodromic and antidromic stimulation, respectively. Extracellular unit activity was recorded from single spinal interneurons with the electrode positioned medial to or on the line of L_7 dorsal root entry and 1.5 to 3.5 mm below the cord surface. The exposed area of the cord was bathed in mineral oil and maintained at 36–37 °C.

[1] T. C. Tseng, A. C. Przybyla, S. T. Chen and S. C. Wang, Neuropharmacology *9*, 211 (1970).
[2] T.C. Tseng and S. C. Wang, J. Pharmac. exp. Ther. *178*, 350 (1971).
[3] D. W. Esplin and E. M. Curto, J. Pharmac. exp. Ther. *121*, 457 (1957).
[4] J. Lewin and D. W. Esplin, J. Pharmac. exp. Ther. *132*, 245 (1961).
[5] H. K. Borys and D. W. Esplin, Neuropharmacology *8*, 627 (1969).
[6] D. W. Esplin and B. Zablocka-Esplin, in *Basic Mechanisms of the Epilepsies* (Eds. H. Jasper, A. Ward and A. Pope, Little Brown and Co., Boston, Mass. 1969) p. 167.

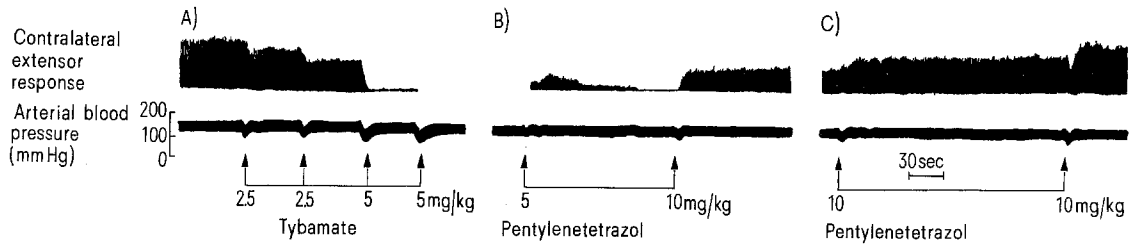

Fig. 1. Effects of tybamate and pentylenetetrazol on contralateral extensor reflex responses in midcollicular cat. A) graded doses of tybamate produce a stepwise reduction in response. B) 20 min following A) – pentylenetetrazol produces some recovery of response. C) 10 min following B) – further administration of pentylenetetrazol results in a reflex response similar to control.

Results and discussion. As shown in Figure 1, A, administration of tybamate reduces the contralateral extensor response in a stepwise manner. Following depression of the contralateral extensor response by tybamate, pentylenetetrazol (5 mg/kg) produced only a transient increase in the reflex. Further administration of pentylenetetrazol to a cumulative dose of 35 mg/kg resulted in a stepwise return of the reflex to control levels (Figure 1, B, C). This depression of the contralateral extensor reflex with tybamate and restoration with pentylenetetrazol could be repeated several times in a single animal.

Subsequent to the above experiments on polysynaptic reflexes we studied the antagonism of these drugs on spinal internuncial neurons. Figure 2 shows the effects of tybamate and pentylenetetrazol on a non-spontaneous firing spinal interneuron. This neuron exhibited repetitive firing in response to dorsal root stimulation. Tybamate (5 mg/kg) abolished the evoked interneuronal activity. Two succeeding doses of pentylenetetrazol (30 mg/kg total) restored activity to slightly above control levels. Further administration of tybamate (5 mg/kg) depressed activity a second time with recovery following an adequate dose of pentylenetetrazol. When given alone, pentylenetetrazol (5–10 mg/kg) consistently produced an increase in firing level.

The above experiments indicate an excitatory effect of parenterally administered pentylenetetrazol on spinal interneuronal activity. This excitatory effect of pentylenetetrazol may explain its effect on the polysynaptic reflex as reported by others[3,4]. Previous observations made by CURTIS et al.[7], using electrophoretically administered pentylenetetrazol, indicate a weak depression of spinal interneuronal activity rather than stimulation as reported here. Their approach, however, is dissimilar in that the action of pentylenetetrazol applied electrophoretically may not be the same as when administered parenterally. Other agents, notably amphetamine[8] and D-lysergic acid diethylamide[9,10], have also been reported to produce opposite effects when electrophoretic application is compared with parenteral administration.

Stimulation of interneurons by pentylenetetrazol is produced by approximately the same dose which consistently excites brain stem neurons[11,12]. Depression of neuronal activity by pentylenetetrazol, observed with 10% of the neurons studied at the level of the brain stem[11] was not observed in this study. Furthermore, depression of interneuron firing rate by the muscle relaxant tybamate was effectively antagonized by pentylenetetrazol on both the contralateral extensor reflex and single spinal interneurons[13].

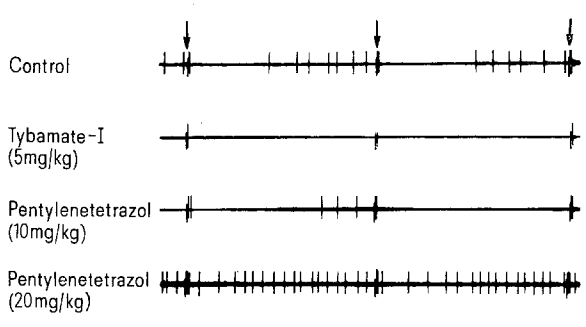

Fig. 2. Effect of tybamate and pentylenetetrazol on a non-spontaneous firing spinal interneuron in an acute high lumbar spinal cat. Potentials were evoked by L_7 dorsal root stimulation. 3 successive reponses are shown (arrows) at a rate of 1 per sec. In this experiments interneuron activity was depressed by tybamate, restored by pentylenetetrazol, depressed a second time with tybamate and restored with pentylenetetrazol.

Zusammenfassung. Das Muskelrelaxans Tybamat ruft eine Hemmung der Aktivität spinaler Interneurone hervor, die von einer Blockade des spinalen polysynaptischen Reflexes begleitet ist. Pentylenetetrazol hingegen hebt die beiden durch Tybamat erzeugten Effekte auf, steigert zudem die interneuronale Aktivität, eine Eigenschaft, die die Verstärkung des polysynaptischen Reflexes erklären könnte.

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[7] D. R. CURTIS, L. HÖSLI and G. A. R. JOHNSTON, Expl Brain Res. *6*, 1 (1968).
[8] P. B. BRADLEY and J. H. WOLSTENCROFT, Br. med. Bull. *21*, 15 (1965).
[9] F. E. BLOOM, E. COSTA and G. C. SALMOIRAGHI, J. Pharmac. exp. Ther. *146*, 16 (1964).
[10] G. K. AGHAJANIAN, W. E. FOOTE and M. H. SHEARD, J. Pharmac. exp. Ther. *171*, 178 (1970).
[11] E. KIRSTEN and E. SCHOENER, Neuropharmacology, *11*, 591 (1972).
[12] K. HIRSH, Ph. D. Dissertation, Columbia University, June 1972.
[13] Supported in part by NSF grant No. GB-29215 and a grant-in-aid from The Eli Lilly Company. E. B. KIRSTEN is the recipient of Career Development Award No. K4-GM 7017901 from the National Institute of General Medical Sciences.