TECHNICAL PAPERS

Effect of Tetraethyl Pyrophosphate on Sympathetic Ganglionic Activity

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This is a further report on the employment of anticholinesterases with reference to the nicotinic effect of ACh, dealing particularly with the most recently discovered antiesterase tetraethyl pyrophosphate (TEP). The nicotinic (ganglionic) effect of various doses of ACh was measured in terms of the pressor response in *atropinized* dogs treated with TEP. Ten γ of TEP/kg. of body weight was sufficient to elicit pressor responses with moderate doses of ACh (0.05–0.10 mg./kg.). With progressively increasing doses of TEP, the pressor response to two standard doses of ACh (0.125 and 0.25 mg./kg.) could be measured, and a curve relating TEP concentrations with the magnitude of the pressor response could be drawn.[1]

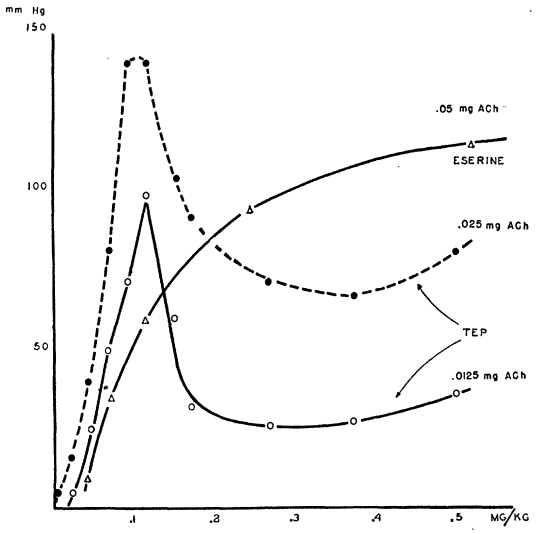

FIG. 1. Pressor response in atropinized dogs to acetylcholine after administration of increasing concentrations of TEP and eserine. (Abscissa—concentrations of the antiesterase in mg./kg.; ordinate—pressor response in mm. of Hg of blood pressure.)

This curve shows two peaks (Figs. 1 and 2), one following the sharp increase in pressor response when from 0.01 to 0.1 mg./kg. of TEP was administered, and another corresponding to the total amount of TEP of 15 mg./kg. A dip of pressor response with a minimum value (varying for individual dogs) for the total concentration of TEP of about 0.25 mg./kg. separates the two peaks. The second peak exceeded the first by some 20–33 mm. of Hg. Continued administration of TEP resulted in diminution of pressor response of ACh until none could be elicited at TEP levels of about 70 mg./kg. Under favorable conditions atropinized dogs survived with as much as 140 mg./kg. Thus, TEP proved to be a more powerful antiesterase than any previously reported. The initial maximal pressor response to ACh appears at the following levels: DFP, 15–20 mg./kg.; eserine, 0.5 mg./kg.; hexaethyltetraphosphate (HETP), 0.5 mg./kg.; and TEP, 0.1 mg./kg. (*5, 7*; see also Table 1).

It has been postulated in a previous communication (*7*) that the measurements of the pressor responses to standard doses of ACh in the presence of varying concentrations of different anticholinesterases could be used as an *in vivo* estimate of the inactivation of the cholinesterase. The present study of TEP further substantiates this assumption. Table 1 compares the estimated concentrations of the different antiesterases necessary to inactivate 50 per cent of the cholinesterase *in vivo* with the results obtained *in vitro* by several investigators. Since the

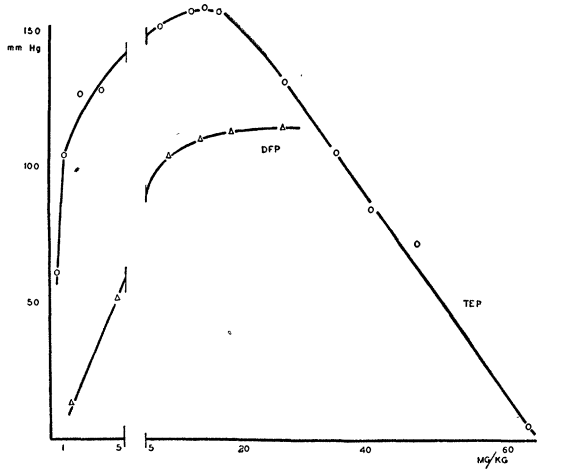

FIG. 2. Pressor response in atropinized dogs to acetylcholine after administration of increasing concentrations of TEP and DFP. Test dosages of acetylcholine: 0.0125 mg./kg. for TEP; and 0.05 mg./kg. for DFP. (Abscissa—concentrations of the antiesterase in mg./kg. Effect of the lower concentrations is not apparent on this scale (cf. Fig. 1); ordinate—pressor response in mm. of Hg of blood pressure.)

latter experimented on animals other than the dog, only a general agreement can be expected. On the whole, the inhibition of the cholinesterase is obtained *in vivo* with smaller concentrations of the antiesterases; thus, the method presented here seems to be more sensitive than the *in vitro* method. At the first peak of the pressor response, representing approximately 100 per cent inactivation point of esterase, TEP seems to be

[1] All drugs were administered in these experiments by injection into the femoral vein. Artificial respiration had to be given to dogs that received more than 1 mg./kg. of TEP.

from two to three times as potent as eserine and HETP and many times as potent as DFP. However, since the early parts of the inactivation curves of cholinesterase by specific antiesterases are steep and differ in character (unpublished results), the comparative estimate of the potency of the anti-

TABLE 1

SENSITIVITY OF ACETYLCHOLINESTERASE TO VARIOUS ANTIESTERASES

	DFP	HETP	Eserine	TEP
	Molar concentrations of inhibitor required to produce a 50 per cent inhibition of cholinesterase activity			
Roach cord (*1*).....	3.0×10^{-6}	4.0×10^{-6}	1.0×10^{-8}	—
Human serum (*6*)..	5.0×10^{-7}	—	5.0×10^{-6}	—
Horse serum (*6*)....	1.3×10^{-8}	—	—	—
Cockroach serum (*3*).....	—	1.0×10^{-7}	—	—
Rat brain (*3*).....	6.3×10^{-8}	1.6×10^{-8}	—	—
Dog (*4, 5, 7*).....	5.0×10^{-9}	4.0×10^{-10}	9.5×10^{-11}	8.5×10^{-11}
	Molar concentrations of the inhibitor required to produce a 100 per cent inhibition of cholinesterase activity			
Rat serum (*3*).....	—	2.0×10^{-9}	—	—
Dog (*4, 5, 7*).....	7.5×10^{-8}	1.0×10^{-9}	7.9×10^{-10}	3.3×10^{-10}

esterases may differ, depending on whether the 50 or 100 per cent inactivation point is taken as the index of activity. (See Table 1, specifically with reference to HETP and eserine.)

The efficiency of TEP seems to be especially remarkable, since in the presence of a wide range of its concentrations as

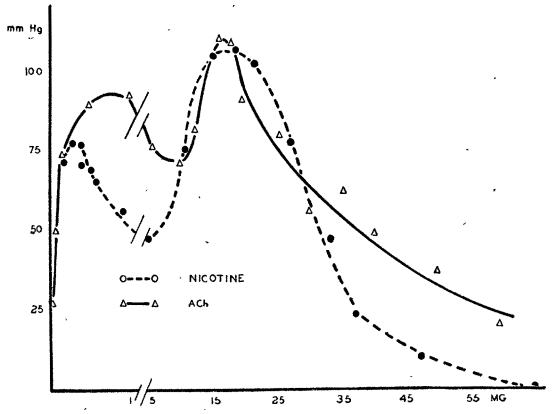

FIG. 3. Pressor response (ganglionic effect) in atropinized dogs to nicotine (0.1 mg./kg.) and acetylcholine (0.05 mg./kg.) (Abscissa—concentrations of eserine in mg./kg.; ordinate—pressor response in mm. of Hg of blood pressure.)

small a dose of ACh as 0.8γ/kg. is sufficient to elicit pressor responses. This figure compares favorably with that of Dale (*2*) of 2γ for the minimum amount of ACh necessary to stimulate on close intra-arterial injection the striated muscle of the frog, and with the minimal amounts previously estimated to be necessary to produce sympathetic ganglionic effects.

The second peak of the pressor response of ACh (Fig. 2), which occurs at considerable levels of TEP ranging from 15 to 20 mg./kg., is of particular interest. A similar peak occurs when the antiesterase used is eserine (Fig. 3; unpublished results). Also, the pressor effects of nicotine itself followed a double-peak curve with increasing amounts of eserine (Fig. 3). It is therefore tentatively suggested that the biphasic response to ACh elicited within a wide range of concentrations of different antiesterases is due to the effect of the latter on the sympathetic ganglia. The ganglia seem to be first depressed, and then, with higher concentrations of the antiesterases, rendered more responsive. Further research must determine whether this effect of the antiesterases on the ganglia is a direct one or related to the mechanism of the synaptic transmission.

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The Influence of Heredity on the Carotene Content of Corn[1]

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The extensive use of hybrid corn in recent years has emphasized the question of possible relationships between the heredity and nutritive content of corn and the possibility of producing hybrids of superior nutritive value. The early work of Hauge and Trost (*2*) pointed out that ordinary genetic factors controlled the vitamin A activity of dent corn, the genes responsible being the same as those governing development of the yellow endosperm. Recently Doty and associates (*1*) have reported that there is some indication that the amounts of the various amino acids in corn protein are related to the genetic constitution of corn hybrids, and that the physicochemical nature of the protein in the grain from two single cross hybrids was distinctly different. In general, however, information is lacking relative to the influence of the genetic constitution of corn on the nutritive value of the grain.

In the course of a comprehensive investigation dealing with this subject, crude carotene values were determined on the grain from all possible single cross combinations of 10 inbred lines of yellow dent corn, all of the same general maturity class and grown during the 1946 season. A 7 x 7 triple lattice design was used in the field experiment, thus providing for analysis three replicate samples of grain for each single cross. The field experiment was conducted near Chambersburg, Pennsylvania, the soil type and fertilizer treatment being the same on the three plots.

The corn was harvested at maturity, and the shelled corn was air-dried at room temperature for 10 days and stored in

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