Protection of Synaptic Transmission Against Block by Nicotine

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During the past year we have studied the effects of various drugs on synaptic transmission in the crayfish; the results will be described elsewhere. In the course of this investigation many drugs were found to have no effect. In such cases a check was made on the preparation by applying a dose of nicotine (10^{-5} grams/cc.) 10 minutes after the original drug. Control tests had shown that nicotine in this concentration blocks transmission in 1–2 minutes. As expected, the presence of most drugs did not influence this action. With some, however, either the nicotine was without effect or the block was greatly delayed. Evidently under certain conditions the preparation is protected against the action of nicotine. Since this situation seems to be of considerable interest, the following preliminary report is presented at this time.

The synapse used in these investigations is between a giant fiber in the central nervous system and a motor fiber in an abdominal root of *Cambarus clarkii* (*3*). The preparation was kept in a bath containing 100 cc. of crayfish perfusion fluid, the drugs being added to this bath. The giant fiber was stimulated between the 5th and 6th abdominal ganglia, while the postganglionic response was led off the 3rd root of the 3rd ganglion. Stimuli were delivered throughout the experiment at 30/minute, at which rate, in the absence of drugs, the postganglionic response remains unchanged for several hours.

The protecting effect was first noted with two drugs, anabasine and nornicotine,[1] which are closely related in structure to nicotine. In a typical experiment, anabasine 10^{-4} was administered. After a transient facilitation, transmission returned to normal. At the end of 10 minutes, nicotine 10^{-5} was given. This had no effect. Ten minutes later, nicotine 10^{-4} was administered, but even this high concentration had no effect for at least 10 minutes.

The results of similar experiments, made with a number of other drugs, permit the following classification to be made:

(a) Drugs which in low concentration protect the crayfish synapse from the action of nicotine, but which block the synapse in higher concentration: anabasine, nornicotine.

(b) Drugs which in subthreshold doses show no protection against nicotine and which block transmission in higher concentrations: alcohol, DFP, eserine.

(c) Drugs which neither protect against nicotine nor block synaptic transmission: acetylcholine, adrenalin, atropine, coramine, picrotoxin, prostigmine, strychnine.

An unexpected result was obtained in experiments in which the nicotine was left in the bath after transmission was blocked. Complete recovery of the root potentials occurred within 40 minutes. Renewed application of nicotine in the same or even higher concentration was now without effect. The same result was obtained when the preparation was washed with fresh perfusion fluid after block by nicotine.

[1] We wish to thank R. C. Roark, Bureau of Entomology and Plant Quarantine, U. S. Department of Agriculture, Beltsville, Maryland, for supplying these drugs.

A similar effect has been observed with eserine. After block by this drug, transmission rapidly returns to normal on washing with fresh fluid. Another dose of eserine, of even higher concentration, is now without effect. The preparation is also protected against the action of nicotine.

Protection against nicotine has been reported by other workers. Novocaine antagonizes the effects of an intravenous injection of nicotine on the heart, blood pressure, and intestine of the dog (*1*). Sulfathiazole inhibits the action of nicotine in the isolated intestine (*2*). The present study, however, has the advantage of confining drug action to synaptic transmission.

Biological competition between structurally related compounds is well known (*4*). In this type of action it is generally considered that the compounds involved compete for attachment to a specific receptor. Such a mechanism is not completely adequate to explain the phenomena described in the present paper, however. Nicotine evidently has a twofold action on synaptic transmission. When first applied, it blocks transmission. As recovery occurs, this blocking action is lost, but a protecting action remains, since further doses of nicotine are without effect. This shift from a blocking to a protecting action suggests that a change takes place in the nicotine molecule by which it becomes ineffective as a blocking agent but remains attached and thereby prevents the action of fresh nicotine. The attachment must involve a firm bond, since washing with perfusion fluid does not interfere with this protection.

Anabasine and nornicotine, which have much less blocking action, seem to attach as readily as nicotine and therefore protect against it. During recovery from nicotine block, nicotine may be transformed into a compound like these or into a related compound with a pure protective action.

References

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Role of Inhibitors in Soybean

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It is now recognized that cooking or autoclaving increases the nutritive value of the protein of soybean. The general opinion is that cooking increases the availability of cystine and methionine. Almquist, *et al.* (*1*) and Hayward and Hafner (*8*) demonstrated that the limiting amino acid in soybean is methionine, and heating under pressure increases the availability of this amino acid. Evans and McGinnis (*4*) found that the retention of organic sulfur is increased from 34 to 52 per cent and that of methionine from 58 to 74 per cent in autoclaved soybean. But Melnick, *et al.* (*9*) found no increase in the retention of methionine in autoclaved soybean, and from their experiments they concluded that the higher biological value of autoclaved soybean was due to an increased rate of release of methionine rather than a higher degree of its availability. Ham and Sandstedt (*6*) found that a dilute acid extract of raw

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