Quebec Cooperative Study
of Friedreich's Ataxia

Pre- And Postsynaptic Effects of Taurine and Gaba in the Cockroach Central Nervous System

B. HUE, M. PELHATE AND J. CHANELET

SUMMARY: *Taurine resembles GABA in its synaptic effects in the cockroach cercal nerve giant fiber synapse where it exerts a depressant action upon synaptic transmission. Both taurine and GABA produce an increased conductance of pre- and postsynaptic membranes through changes in the permeability of chloride ions.*

RÉSUMÉ: *La Taurine ressemble de près au GABA dans son action sur le synapse géant de la blatte, où les deux substances produisent une dépression de la transmission synaptique. La Taurine et le GABA produisent une augmentation de la conductance des membranes pré- et postsynaptique par leur effet sur la perméabilité des ions de chlore.*

From le Département de Physiologie, Faculté Mixte de Médecine et de Pharmacie, Centre Universitaire d'Angers, France

Reprint requests for the complete supplement on Friedreich's Ataxia (Phase Two, Part Two) to:

Dr. André Barbeau, M.D., Clinical Research Institute of Montreal, 110 Pine Avenue West, Montreal, Quebec, Canada, H2W 1R7.

INTRODUCTION

Taurine and γ-aminobutyric acid have been shown to be involved in inhibitory mechanisms in vertebrate and invertebrate nervous system (Curtis and Watkins, 1965). Analysis of synaptic effects of amino-acids are well known at peripheral synapses (Dudel, 1965; Takeuchi and Takeuchi, 1975; Constanti, 1977). Other studies at the unitary level in the sixth abdominal ganglion of the cockroach (Callec, 1974), in bullfrog spinal ganglion (Nishi et al., 1974), in rat spinal ganglion (Deschesnes et al., 1976) and cat spinal ganglion (Gallagher et al., 1978) have generated much data concerning the site and/or the ionic basis of the action of γ-aminobutyric acid.

Previous results have respectively demonstrated the lack of effect of taurine on the cockroach giant axon (Pelhate et al., 1978) and its depressant action on the cockroach cercal-nerve giant fiber synapse (Hue et al., 1978). These findings have led us to investigate in further detail the effects of taurine and γ-aminobutyric acid on the afferent and efferent pathways located in the sixth abdominal ganglion of the cockroach (Periplaneta americana).

METHODS

Experiments were performed on adult male cockroaches. The methods (oil-gap and mannitol-gap techniques) used to investigate the amino-acid sensitivity of the cockroach cercal nerve giant fiber synapse have been described in detail previously (Pichon and Callec, 1970; Callec and Satelle, 1973; Callec, 1974; Hue et al., 1976, 1978). In addition the record of the presynaptic terminal polarization was made with the mannitol-gap apparatus (we have adapted that technique to the presynaptic cercal nerve XI which contains many cholinergic fibers).

Polarization of pre- and postsynaptic membranes was continuously monitored on a rectilinear ink writing paper recorder. Postsynaptic events were observed on storage and conventional oscilloscopes, and results were stored on a magnetic tape recorder or filmed immediately with a camera.

In some experiments postsynaptic events were computed using a programmable signal analyser (Histomat S) and presented as a mean of 3 to 50 signals (see fig. 1 and 5).

All experiments were carried out at constant room temperature (18° C). A Ringer solution (Ri) containing 210 mM NaCl, 3.1 mM KCl, 5.4 mM $CaCl_2$ was applied continuously to the desheathed sixth abdominal (A6) ganglion. The pH value was adjusted to 7.2 with a phosphate-bicarbonate buffer.

Taurine (Merck,) γ-aminobutyric acid (Sigma) were used in addition to the Ringer. When testing the interaction of picrotoxin and/or strychnine with taurine and γ-aminobutyric acid, the amino acids were added to the picrotoxin and/or strychnine solution. In some experiments, in order to study the eventual chloride dependency of taurine and/or γ-aminobutyric acid responses, the chloride content of the standard Ringer solution was reduced by replacement of a portion of the sodium chloride with equimolar sodium acetate.

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GABA and Taurine log-dose response curves were obtained using non-cumulative external applications (Feltz, 1971; Constanti, 1977).

*Drug abbreviation: Tau. = Taurine; GABA = γ-aminobutyric acid; PTX = Picrotoxin; STRY = Strychnine.

RESULTS

1- Comparative effects of Tau. and GABA on evoked EPSP amplitude.

Tau. is known to mimic the action of GABA in nervous tissues. At the cercal-nerve giant-fiber synapse, no quantitative studies have been made. In order to study the potency of Tau. and GABA to depress the synaptic transmission, preliminary experiments were performed using the mannitol-gap technique at the postsynaptic level. Evoked excitatory postsynaptic potentials (EPSP) and continuous postsynaptic polarization were recorded on a magnetic tape. The analysis of Tau. and GABA-mediated potential changes was done later on a programmable Histomat S signal analyser. Fig. 1 gives an example indicating the stronger synaptic depressant effect on Tau. compared to GABA's at the same concentration : 10 mM. On the other hand Tau. and GABA induced a postsynaptic hyperpolarization (see fig. 1 and Table 1).

Are Tau. and GABA acting on the same or different membrane receptors? In order to answer this question, experiments were performed using the single-fiber oil-gap technique. This unitary technique allows the control of the postsynaptic membrane resistance by passing pulses of hyperpolarizing current using a Wheatstone bridge circuit. Control of the evoked EPSP amplitude can be achieved at the same time.

Fig. 2 shows semi-logarithmic dose-responses curves in which the postsynaptic resistance decrease was plotted versus the logarithm of the amino-acid concentration. Results were obtained using non cumulative application of amino-acid. GABA often produced responses which faded during the drug application; for this reason we have taken the maximal effect of the drug. Comparable studies were made using the evoked EPSP amplitude as a test of amino-acid effect. Results appear in fig. 3.

The results of the experiments illustrated in fig 2 and 3 and data enclosed in Table I suggest that Tau. is a more potent compound than GABA to depress the evoked EPSP, whereas the effects of GABA on the postsynaptic membrane resistance are more important than those obtained with Tau.

In order to clarify the nature of the receptor mechanism involved in Tau. we have studied the combined application of GABA and Tau. on a single postsynaptic fiber. The control GABA curve was compared with curves obtained by combining varying concentrations of GABA with 2.5 and 10mM of Tau. GABA "combination" curve obtained was shifted upwards in a non parallel manner. According to the "occupation theory" (Ariens and Simonis, 1964) Tau. appears to be an agonist of GABA at this level. (Fig. 4 and 5)

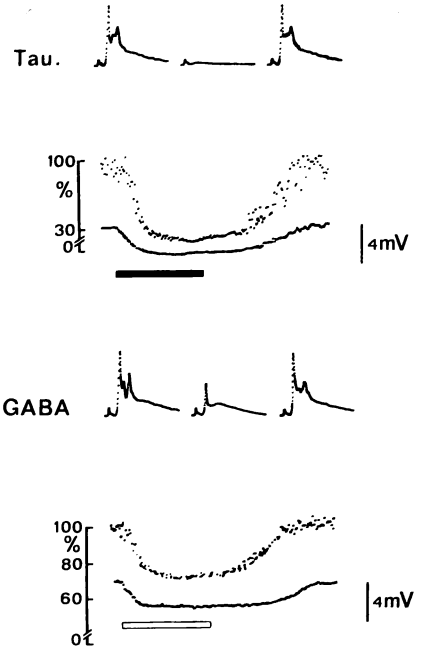

Figure 1. — Effects of Tau. (10mM) and GABA (10 mM) on the evoked EPSP amplitude and postsynaptic polarization. (mannitol-gap technique). Graphs are issued from the Histomat signal analyser and drawn with an XY writing table.

For each amino-acid, the mean of 30 postsynaptic responses before, during and after the effect is represented (upper trace).

Below, the time course of the evoked EPSP amplitude is shown (scale on the left indicates the percentage of the remaining EPSP). The third line depicts the evolution of the postsynaptic polarization (scale on the right). Each point of the second and third line represents the mean issued from 3 postsynaptic events.

Black and white bars denote period (5 mn) of application of amino-acids.

TABLE I

N° Experiment	%tage of variation after 15 minutes of experiment -(increase) +(decrease)									
Oil-gap technique	Control		Tau 20 mM		GABA 20 mM		Tau+GABA		GABA+Tau	
	Rmb	EPSP ampl.	Rmb	EPSP ampl.	Rmb	EPSP ampl.	Rmb	EPSP ampl.	Rmb	EPSP ampl.
1	+2%	0	-26,8%	-74%	-34,8%	-23,5%	-60,2%	-75,3%	62,4%	-78,6%
2	0	0	-20%	-76%	-30%	-25,2%	-50,7%	-78,1%	52%	-78,8%
3	-2%	-3%	-23%	-81%	-32,2%	-26,4%	-57,3%	-89,8%	-56,2%	-90,2%
4	+1%	+2%	-17%	-72%	-29,2%	-25,8%	-50,2%	-75,1%	-49,8%	74,3%
5	0	0	-28%	-80%	-35%	-27,2%	-62,4%	-87%	-63,1%	-88,2%
Average	+0,2%	+0,2%	-22,96%	-76,6%	-32,24%	-25,62%	-56,16%	-81,06%	-56,7%	-82,02%

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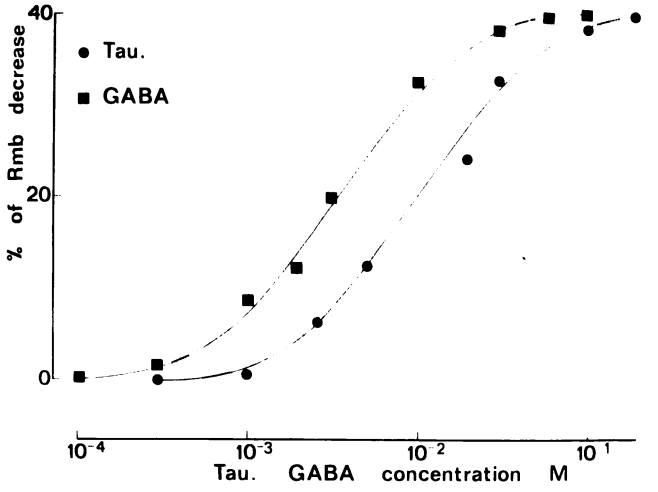

Figure 2. — Effects of Tau. and GABA on the postsynaptic membrane resistance (Rmb). No — normalized curves.

The same maximal decrease of Rmb (40%) is obtained under Tau. or GABA treatment.

Dose-response curves are issued from a representative experiment. Single-fiber oil-gap technique.

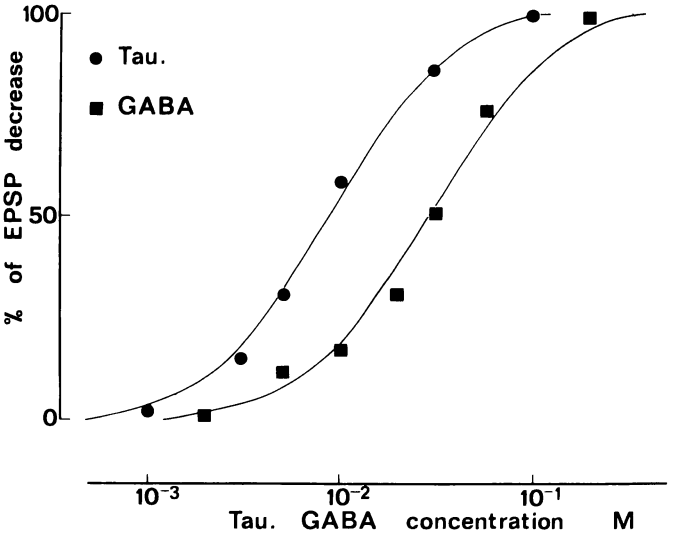

Figure 3. — Effects of Tau. and GABA on the evoked EPSP amplitude. The normalized decrease of the EPSP is plotted versus the logarithm of Tau. and GABA concentration. Singlefiber oil-gap technique.

2- Presynaptic effects of Tau. and GABA

Pharmacological investigations at the presynaptic level can be done using the preparation including the cercal nerve XI and the postsynaptic giant axon. For this, we have used the mannitol-gap technique previously described. Recording of the polarization of the presynaptic fiber was made between the end of the cercal nerve XI and the A6 ganglion, which is connected to the ground.

In normal conditions Tau. 20 mM and GABA 20 mM produced a depolarization of about 1.5 mV on the afferent pathways included in the cercal nerve XI. On the other hand, effects of amino-acids have been tested on degenerated cercal nerve XI. Degeneration was obtained by cutting the nerve at the basis of the cercus, 15 days before the test. Under these conditions, the presynaptic effects of Tau. and GABA are abolished. These last data enhance the suggestion of a presynaptic depolarizing effect of Tau. and GABA.

As seen in fig. 6 these experiments have been completed by a test of combined solutions (GABA + Tau.) which are active on the presynaptic polarization. Nevertheless, at this level, it is not possible to be precise about the direct effect of Tau. and GABA upon the membrane resistance. Presynaptic depolarization was taken as a test of increased membrane conductance. By analogy with the postsynaptic effect of combined solutions we could expect the same synergistic effect of Tau. at the presynaptic level.

In an earlier report (Hue et al., 1978) we had suggested a presynaptic action of Tau. i.e. a weak decrease of the presynaptic action potential. In order to delineate and compare this putative effect, we have recorded and stored on a magnetic tape the electrotonically transmitted presynaptic action potentials, triggered by strong electrical presynaptic stimulations, in standard Ri and under Tau. and GABA treatment. Fifty signals were computed and averaged in each case. The results presented in fig. 7 are in accordance with the wealth of evidence for the generally accepted view that the presynaptic spike decrease is the result of presynaptic Tau. or GABA-induced depolarization. Nevertheless, the presynaptic spike being recorded by electrotonic transmission and the decrease of the postsynpatic membrance resistance could partially explain the presynaptic spike decrease.

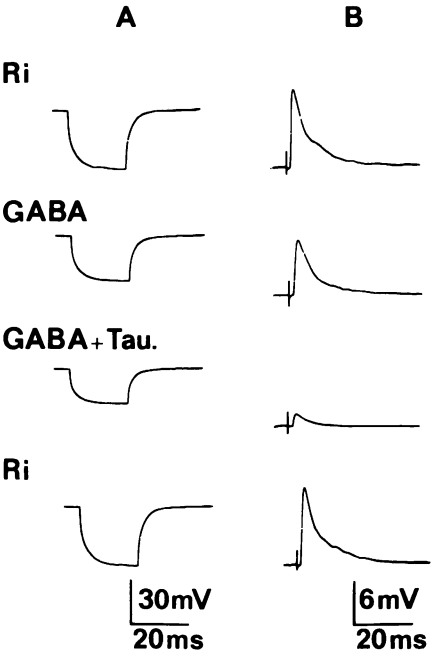

Figure 4. — Effects of Tau. 10 mM and combined solutions Tau. 10 mM +GABA 20 mM on the postsynaptic membrane resistance (A) and evoked EPSP (B).

Resistance was tested as an hyperpolarizing current pulse applied through the postsynaptic membrane. EPSP was evoked by a presynaptic electrical stimulation applied on the homolateral cercal nerve XI.

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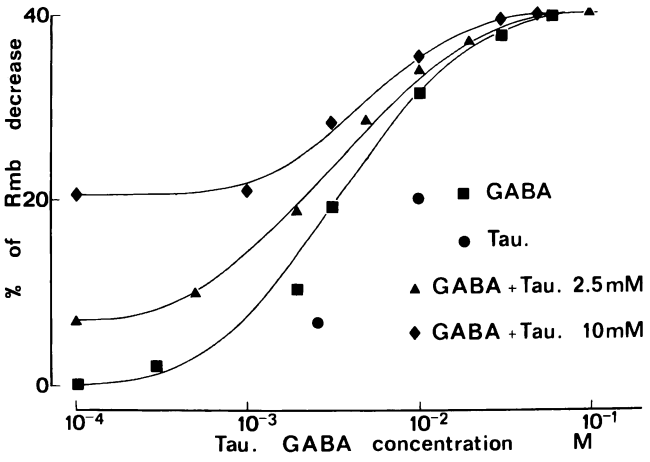

Figure 5. — Interaction between GABA and Tau. on the postsynaptic membrane resistance (Rmb). Varying concentrations of GABA are applied with a fixed dose of Tau. 2.5 and 10 mM. Results obtained were compared with the normal dose-response curve. Note the upward non-parallel shift of the combined curves. No-normalized curves.

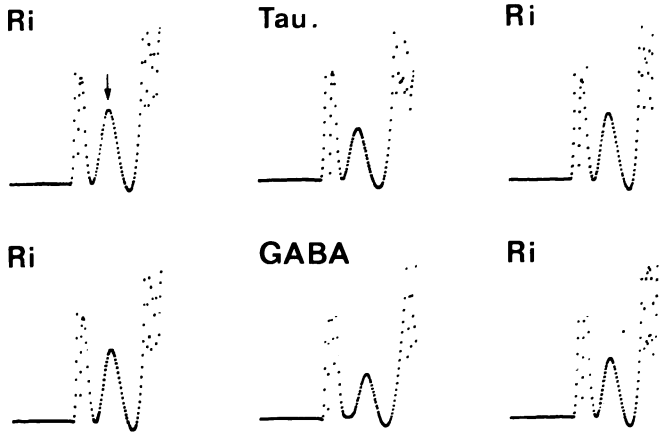

Figure 7. — Effects of Tau. 20 mM and GABA 20 mM on the electrotonically transmitted presynaptic action potential (arrow).

Synaptic events are issued from mannitol-gap technique, stored on a magnetic tape, computed and presented in form of dot-display recordings as a mean of 50 signals.

Note that the induced Tau. and/or GABA decrease of the presynaptic spike is reversible by washing with normal Ri.

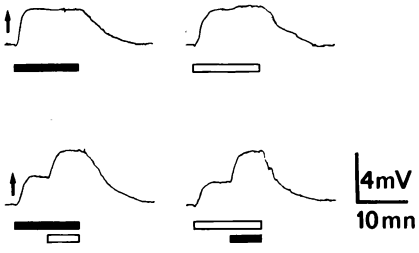

Figure 6. — Effects of Tau. 20 mM (black bars) and GABA 20 mM (white bars) and combined solutions on the presynaptic fiber polarization. Arrow indicates the depolarizing direction from a stable resting polarization.

Presynaptic fiber polarization was recorded using the mannitol-gap technique.

3-Chloride and potassium dependency of pre- and postsynaptic effects of Tau. and GABA.

Experiments were performed with standard Ri and low chloride solutions as indicated in fig. 8 et 9. Results are consistent with the hypothesis of an increase in pre- and postsynaptic membrane permeability to chloride ions for both, Tau. and GABA. It appears therefore in both cases, that the presynaptic chloride dependency corresponds via a shift to the left of the postsynaptic chloride dependency linear relationship.

For the potassium dependency of Tau. and GABA effects, the results of some experiments (not illustrated here) in which external potassium was increased, lead us to conclude that Tau. and GABA allowed a weak increase in potassium permeability of pre- and postsynaptic membranes.

4- Action of antagonistic substances: Picrotoxin and Strychnine

According to numerous findings, PTX which is known as an antagonist of GABA (Takeuchi and Takeuchi, 1969; De Groat, 1972; Levy and Anderson, 1972; Barker et al., 1975 a) has also an antagonistic action to Tau. (Barker et al., 1975; Koidl and Florey, 1975; Nistri and Constanti, 1976). At the cercal-nerve giant-fiber synapse of the cockroach, Callec (1974) has shown that PTX was able to suppress spontaneous and evoked IPSP and to enhance the subthreshold evoked EPSP (see also fig. 10).

On the other hand, STRY which is known to block spinal inhibition postsynaptically by interacting with glycine receptors (Curtis et al., 1971), has been reported to antagonize Tau. effect (Barker et al., 1975 a, b; Nistri and Constanti, 1976). At the crayfish neuromuscular junction (Parnas and Atwood, 1966) and at the cockroach neuromuscular junction (Atwood and Jahromi, 1967) STRY has been found to block the synaptic transmission by acting on the presynaptic endings. We have shown in fig. 10 that an irreversible block of the cercal-nerve giant-fiber synapse occurs during application of STRY 10^{-4} M.

In the experiments described here, PTX was employed at various concentrations and applied 20 minutes before the amino-acid test. Results summarized in fig. 11 and 12 show that Tau. responses were more antagonized by PTX than GABA responses and were completely suppressed at 10^{-5} M PTX. In other respects, in some experiments, we have noted that PTX 10^{-7} M to 5 x 10^{-7} M does not strongly antagonize the Tau.-induced postsynaptic resistance change but partially antagonizes the important depressant effect of Tau. on the evoked EPSP amplitude. Perhaps there is a particular antagonistic action of PTX which explains the different potencies of Tau. and GABA to depress the evoked EPSP amplitude.

In many cases, especially high concentrations of PTX increased the postsynaptic membrane resistance (see Callec, 1974) by 10 to 20% and inhibited all the effects of Tau. and GABA.

In some experiments the interaction between STRY and GABA and/or

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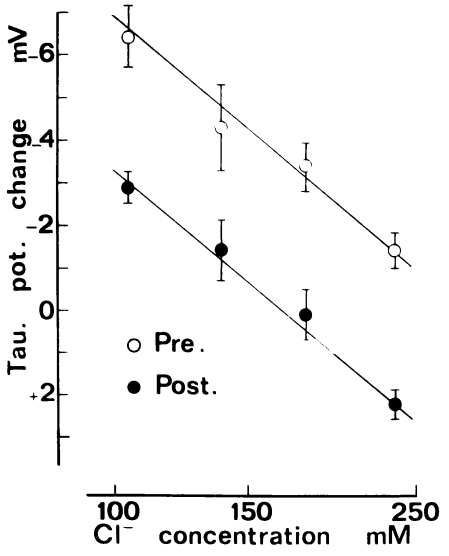

Figure 8. — Pre- and postsynaptic potential changes during addition of Tau. 20 mM to Ringer solution containing a various amount of chloride. Mannitol-gap technique.

Each point represents the average of six to fifteen values (±S.E.).

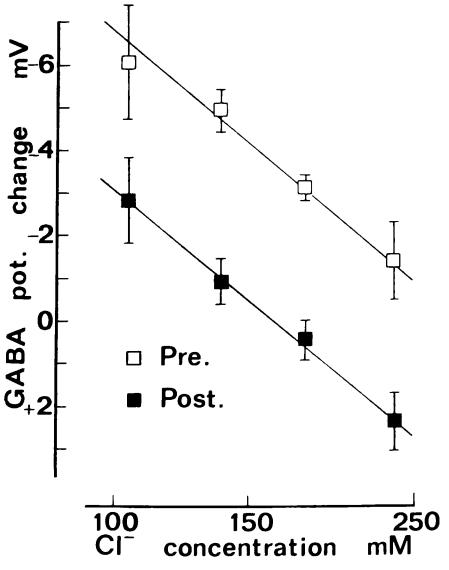

Figure 9. — Pre- and postsynaptic potential changes during addition of GABA 20 mM to Ringer solution containing a various amount of chloride. Mannitol-gap technique.

Each point represents the average of five to eight values (±S.E.).

Tau. was tested on the Tau. and GABA postsynaptic resistance changes. Increasing concentrations of STRY were applied on the A6 ganglion and Tau. or GABA tests were done after 30 minutes of pre-treatment with the drug. Tau. responses apear reduced by strychnine while GABA's are not affected. Nevertheless, high doses of strychnine are required to antagonize Tau. responses.

DISCUSSION

The results of the experiments presented here demonstrate that synaptic transmission in the insect central nervous system is affected by Tau. and GABA (Callec, 1974).

Earlier results of the Tau. effects have been published (Hue et al., 1978) but no quantitative study and comparison with the GABA effects have been made. Callec (1974) has shown that GABA was able to block the cercal-nerve giant-fiber synapse and was antagonized by PTX. In a previous report (Hue et al., 1978), we presented the evidence that Tau. may depress the synaptic transmission in the same preparation.

In the cockroach A6 ganglion Tau. was a more potent compound than GABA in blocking synaptic transmission. If under GABA treatment the slight decrease of EPSP amplitude can be interpreted as due to change in postsynaptic membrane resistance (Callec, 1974), our data for Tau. show an identical or a lower decrease in postsynaptic membrane resistance involve a major reduction of EPSP amplitude (fig. 1, 2 and 3). These results suggest that Tau. acts on EPSP amplitude by a passive effect on the postsynaptic membrane resistance like GABA, but, in addition another mechanism must be required to explain the strong effect of Tau. on EPSP amplitude.

The observed depolarization of presynaptic terminals induced by Tau. and GABA is in agreement with the literature (Schmidt, 1963; Dudel, 1965; Tebecis and Phillis, 1969; Davidson and Southwick, 1971; Davidoff, 1972; Nishi et al., 1974; Barker et al., 1975 a; Gallagher et al., 1978). According to these authors, it is possible to explain the weak decrease of the presynaptic action potential by the Tau. and/or GABA induced presynaptic terminal depolarization. This depolarization and especially the associated increase of presynaptic membrane conductance to chloride ions would shunt the presynaptic action potential amplitude. When one knows the importance of the amplitude of presynaptic spike on the influx of calcium governing the process of transmitter release (Katz et Miledi, 1967) we should expect a reduction in transmitter release by Tau. or GABA action at the presynaptic level.

The dose-conductance relationships obtained with GABA and Tau. suggest for both the same intrinsic activity, but a lower affinity for Tau. However the receptor mechanism of Tau. effect remains unclear. On the one hand GABA/Tau. "combination" curves obtained are similar to those obtained with GABA/5-aminovalerianic acid at the lobster inhibitory neuromuscular junction by Constanti (1977). In this case we should expect an agonist effect for Tau. On the other hand 5-aminovalerianic acid is part of a group which has in common with Tau. and β-alanine antagonism to STRY and PTX (Barker et al., 1975 a). In addition, at the cercal-nerve giant fiber synapse we have noted that STRY antagonizes only Tau. and that PTX is able to antagonize in varying degrees both Tau. and GABA responses. These last results are similar to those obtained at the crayfish neuromuscular junction (Dudel, 1965), at the rat superior cervical ganglion (Bowery and Brown, 1974) and in the frog spinal cord (Barker et al., 1975 a).

The ionic mechanism whereby Tau. and GABA produce an increased conductance of pre- and postsynaptic membranes involves primarily chloride ions. This is supported by the direct dependency of the responses to Tau. and/or GABA application in low chloride solutions. A linear relationship was obtained both at the pre- and postsynaptic levels. The behavior of presynaptic terminal varying in a parallel manner in various chloride solutions suggests that Tau. and/or GABA cause a comparable increase in presynaptic membrane permeability to chloride ions. The parallel shift of the Tau. and GABA potential changes in the presynaptic fiber raises a question relating to the different

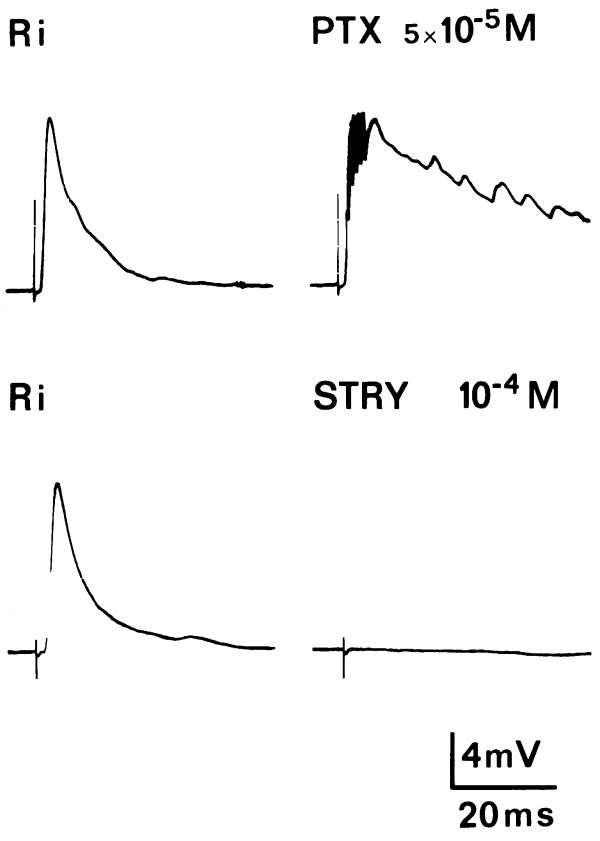

Figure 10. — Effects of PTX and STRY on the evoked EPSP in the A6 ganglion. Single-fiber oil-gap technique.

After 30 minutes of PTX treatment, the evoked EPSP is increased both in amplitude and duration and is able to trigger repetitive action potentials (which appears truncated) in the giant axon.

STRY 10^{-4} M blocks irreversibly the synaptic transmission in less than 20 minutes.

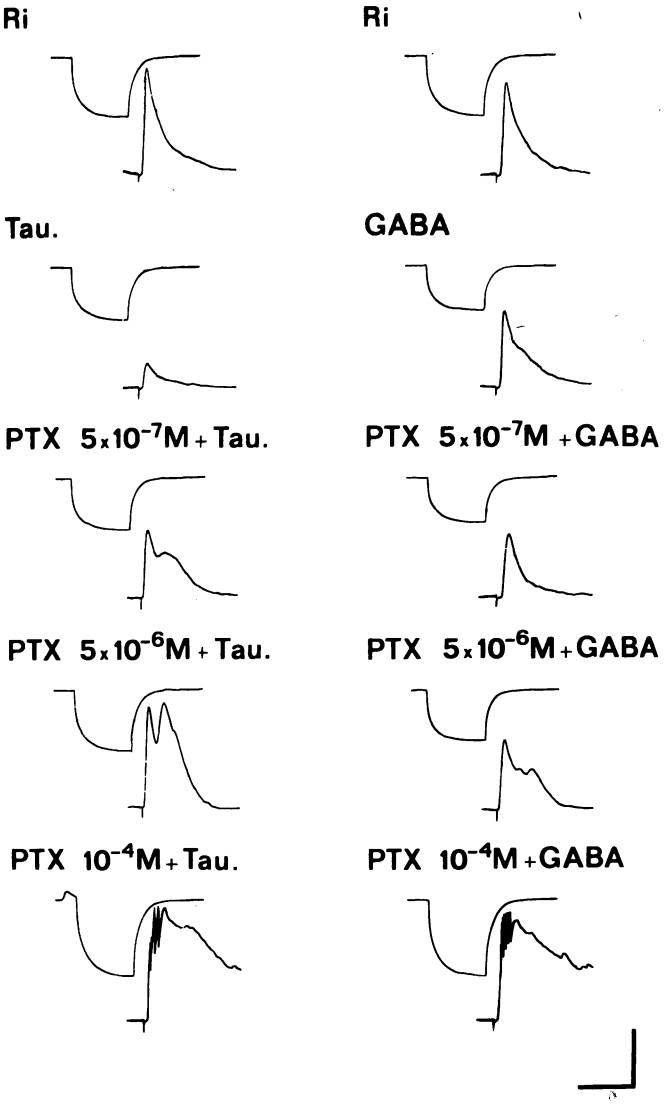

Figure 11. — Effect of Tau. and GABA on postsynaptic resistance and evoked EPSP amplitude before and after a 20 minutes PTX pretreatment of the A6 ganglion.

— Note the beginning of the antagonistic effect of PTX 5 x 10^{-7} M to Tau.-reduced EPSP, and the increase of postsynaptic membrane resistance under PTX 10^{-4} M treatment.

Horizontal scale: 20 ms

Vertical scale: 40 mV for hyperpolarizing pulses
8 mV for EPSP

responses of the pre- and postsynaptic membranes to Tau. and GABA in various chloride solutions. Why are such responses opposite at the pre- and postsynaptic level, if one obtains in both cases an increase in membrane chloride permeability? A simple explanation may be that the intracellular chloride concentration is relatively higher in the presynaptic terminal. One would suppose the presence in these presynaptic fibres of a metabolically dependent inwardly directed chloride pump. Such a mechanism has already been suspected in various preparations (Keynes, 1962; De Groat, 1972; Nishi et al., 1974).

However, the possibility that movements of other ions are involved in Tau. and GABA responses cannot be excluded. Following a 2 fold increase of external potassium concentration (from 3.1 to 6.2 mM), the Tau. and GABA induced postsynaptic hyperpolarizations decreased slightly in amplitude.

In conclusion, a similarity has been observed between Tau. and GABA in their effects on ion conductance changes. For Tau. there is a greater potency to block the cercal-nerve giant-fiber synapse. According to several authors who have studied. the ganglionic action of homotaurine and Tau. (De Groat, 1970; Horii et al., 1971; Hilton, 1977), the effects of Tau. on cholinergic receptors cannot be eliminated.

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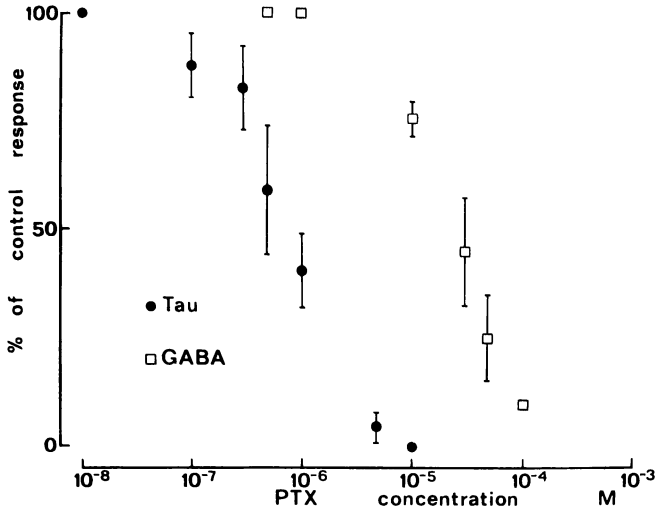

Figure 12. — Effect of increasing concentrations of PTX on Tau. and GABA responses.

The Tau. and GABA induced postsynaptic resistance changes, expressed as a percent of control, are plotted against the logarithm of the PTX concentration.

Each point represents the mean±S.E. of two to six values.

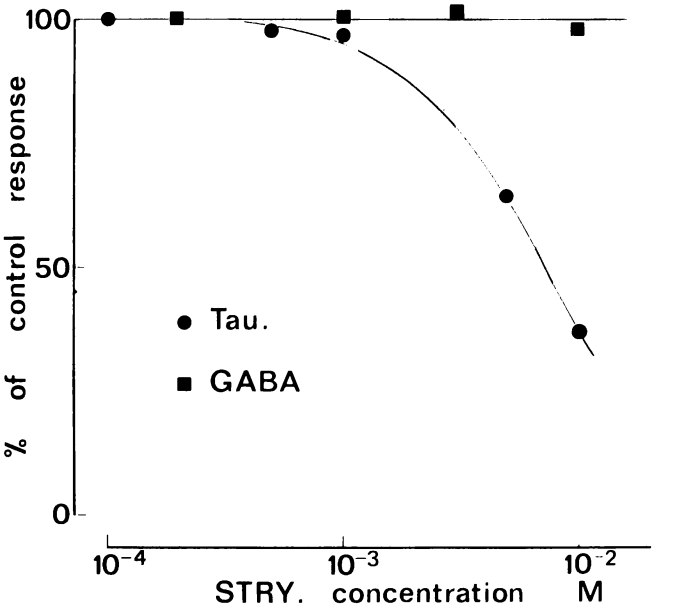

Figure 13. — Effects of increasing concentrations of STRY on Tau. and GABA responses.

The Tau. and GABA induced postsynaptic resistance changes, expressed as a percent of control, are plotted against the logarithm of the STRY concentration.

Results are issued from a representative experiment.

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