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The Effects of Cyanide on Neural and Synaptic Function in Hippocampal Slices

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ABSTRACT: Transverse slices from guinea pig hippocampi were exposed to micromolar concentrations of sodium cyanide while neural and synaptic function were monitored in the CA1 region. Cyanide concentrations between 10 and 200µM rapidly depressed synaptic transmission between Schaffer collateral-commissural fibers and CA1 pyramidal cells. Analysis of input/output curves revealed that the suppression had two components, a decrease in EPSP generation and an increase in action potential threshold. Direct electrical excitability of axons was not affected. At concentrations to 500µM, cyanide had no effect on antidromic activation of pyramidal cells. At 1000µM, cyanide caused a moderate depression of the antidromic response in one slice while having no effect in one other. In some experiments, postsynaptic responses in the gyrus dentatus (GD), evoked by perforant path stimulation, were recorded simultaneously with CA1 responses during cyanide application. GD was found to be less sensitive to cyanide than CA1. All cyanide effects reversed rapidly and completely upon washout. These findings suggest that cyanide has a direct effect on neurons not mediated by its inhibition of metabolism. © 1989 Intox Press, Inc.

INTRODUCTION

Although the physiological actions of cyanide in altering respiratory frequency had been known for some time, it was only in 1876 that Hoppe-Seyler demonstrated that cyanide causes a reversible inhibition of oxidation reactions in tissue. That the mechanism of this effect was due to inhibition of cytochrome *c* oxidase was first shown by Keilin (1925) and later confirmed and expanded by numerous investigations (e.g., Warburg, 1931; Keilin and Hartree, 1938; Albaum et al., 1946; Camerino and King, 1966; Schubert and Brill, 1968; Ballantyne et al., 1972; Piantadosi et al., 1983; Jones et al., 1984).

Acute cyanide intoxication rapidly produces a variety of clinical symptoms. Mild poisoning causes vertigo, headache, and weakness sometimes accompanied by nausea. More severe exposure causes a variety of symptoms including dyspnea, loss of coordination of movements, palpitation and syncope, and convulsions, leading to coma and death due to respiratory failure (Wolfsie and Schaffer, 1959;

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TABLE 1. Number of slices showing total, partial, or no depression of synaptic transmission in different cyanide concentrations. Synaptic depression was categorized in terms of the response to a stimulus that evoked a population spike 80 - 90% of maximal before cyanide exposure. If after 20 min of cyanide exposure the same stimulus evoked a population spike 90% or greater of the control value, synaptic depression was classified as "none"; if between 5 and 89% of control, "partial", if less than 5% of control, "total".

Cyanide Concentration	Level of Depression		
	None	Partial	Total
5 (n=4)	4 (100%)	0	0
10 (n=3)	2 (67%)	1 (33%)	0
25 (n=3)	1 (33%)	2 (67%)	0
50 (n=5)	0	5 (100%)	0
100 (n=8)	0	7 (88%)	1 (12%)
200 (n=4)	0	0	5 (100%)

TABLE 2. Mean Areas ($\pm$ SEM) of Component I/O Curves During Cyanide Application, Expressed as a Fraction of Control Area (as defined in text).

Input-Output	100 μM	50 μM	25 μM
	n = 6	n = 5	n = 3
St-PV	1.04 ± 0.04	1.15 ± 0.06	0.96 ± 0.06
St-EPSP	0.82 ± 0.03**	0.86 ± 0.06*	0.80 ± 0.12*
St-PS	0.30 ± 0.27**	0.59 ± 0.05**	0.65 ± 0.36*
PV-EPSP	0.79 ± 0.03**	0.79 ± 0.06**	0.90 ± 0.11
PV-PS	0.28 ± 0.24**	0.47 ± 0.05**	0.69 ± 0.33*
EPSP-PS	0.36 ± 0.33**	0.61 ± 0.08**	0.86 ± 0.22

St = stimulus current; PV = presynaptic volley; EPSP = focally recorded excitatory post-synaptic potential; PS = population spike. *$p < 0.05$ **$p < 0.01$ (Student's T test).

Graham et al., 1977; Egekeze and Oehme, 1980; Ballantyne, 1983).

The symptoms of acute cyanide exposure occur quite rapidly, particularly when the toxin is administered as hydrogen cyanide gas. The exact mechanisms by which these symptoms are induced are not understood. While cyanide's inhibition of oxidative metabolism is

firmly established, the nature and rapidity of the symptoms are also consistent with a direct, nonmetabolic effect of cyanide on the central nervous system. Such an effect, if present, would act in concert with the metabolic inhibition to contribute to cyanide's rapid lethality.

To investigate this possibility we have examined the effects of acute cyanide exposure on neural and synaptic function in hippocampal tissue slices maintained *in vitro*. The cyanide concentrations used in these experiments (5 - 1000 µM) span the range of concentration found in brain tissue of animals killed by cyanide intoxication (8 - 42 µM) (e.g., Ballantyne *et al.*, 1972; Ballantyne and Marrs, 1987).

METHODS

Hartley guinea pigs (300 - 400 gm) were deeply anesthetized with ether, decapitated, and the brain removed and rapidly chilled. One hippocampus was dissected free and cut into transverse slices 0.4 mm thick, which were maintained in a holding chamber at room temperature for 1-6 hr before being transferred to the recording chamber. In the recording chamber, 1 or 2 slices were supported on a nylon mesh, totally submerged under artificial cerebrospinal fluid (ACSF) flowing at 1.4 - 1.6 cc/min (temperature 32°C). The ACSF contained, in millimoles, NaCl 124, KCl 5.0, NaH$_2$PO$_4$ 1.25, MgSO$_4$ 2.0, CaCl$_2$ 2.0, NaHCO$_3$ 26.0, dextrose 10.0, and was continuously bubbled (in the supply reservoir) with 95% O$_2$ - 5% CO$_2$ (pH 7.35-7.45).

A cyanide solution was prepared by dissolving reagent grade sodium cyanide in fully oxygenated ACSF to a concentration of 1 - 4 mM. This stock solution was kept in a full or almost full sealed container and diluted to the desired final concentration with additional fully oxygenated ACSF immediately before application to the slices. (At pH's in the physiological range, cyanide can be lost from solution as HCN. While we kept our cyanide solutions sealed as much as possible, some cyanide was undoubtedly lost during actual cyanide application to slices. All we can say for sure is that

the actual cyanide concentrations seen by the tissue were lower than calculated.)

Extracellular field potentials were recorded with glass microelectrodes in stratum (st.) pyramidale and/or st. radiatum of the CA1 region. Monopolar tungsten electrodes were used to deliver constant current stimulating pulses to the Schaffer collateral-commissural fibers in st. radiatum (for orthodromic stimulation) and/or the CA1 pyramidal cell axons in the alveus (for antidromic stimulation). In a small number of experiments, simultaneous recordings were made in the gyrus dentatus (GD) by stimulating the perforant path and recording the postsynaptic population spike in st. granulosum. Evoked waveforms were digitized and stored for later analysis. A semi-automated computer program measured the following variables: (1) the peak-to-peak amplitude of the compound action potential of the afferent fiber tract (the presynaptic volley, or prevolley), (2) the maximum slope of the focally recorded excitatory postsynaptic potential (EPSP), and (3) the amplitude of the postsynaptic compound action potential (population spike).

Input/output (I/O) curves were generated by delivering stimulus pulses over a range of intensities from subthreshold to supramaximal, and plotting the following relationships: (A) The population spike as a function of either stimulus intensity or of prevolley, (B) The prevolley as a function of stimulus intensity, (C) The EPSP as a function of prevolley, and (D) The population spike as a function of EPSP. Relationship (A) is the classical I/O curve (Rall, 1955) and provides a measure of the overall effectiveness of synaptic transmission. Relationship (B) reflects the electrical excitability of the presynaptic fibers. Relationship (C) reflects presynaptic transmitter release and the response of the postsynaptic membrane to the released transmitter. Relationship (D) reflects the overall excitability, or threshold, of the postsynaptic pyramidal cell population. In some experiments, the antidromic stimulus-response curve (antidromic population spike vs. stimulus intensity) was also plotted.

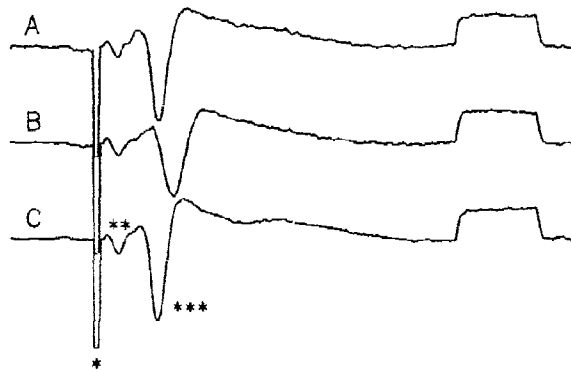Two basic experimental protocols were used. In one, the ortho- and/or antidromic

FIG. 1. Unaveraged waveforms recorded from stratum pyramidale of CA1 in response to 500μA stimulation pulses. A: Control. B: During exposure to 50 μM cyanide. C: Wash. (*) stimulation artifact, (**) initial EPSP rise, (**) population spike. Square wave calibration pulse at end of each tracing: 1mV 5mS.

stimulation intensities that evoked a population spike 70-80% of maximal were determined, and the slice was stimulated at these intensities, once every 20 or 30 sec, over the course of the entire experiment. Response amplitudes were plotted as a function of time, before, during, and after cyanide application. The second protocol, done in CA1 only, generated I/O curves before, during, and after cyanide application. In some cases the two protocols were combined, with the continuous stimulation interrupted for I/O curve generation. Cyanide was bath-applied for periods ranging from 20 - 45 min.

To quantify changes in I/O curves, a single numerical score was obtained for each I/O curve by calculating the area bounded by the curve and the X axis (Balestrino *et al.*, 1986; Skelton *et al.*, 1983). For each triplet of I/O curves (pre-cyanide, experimental, recovery), areas were calculated over the same range of abscissal values, i.e., from 0 to the largest abscissa present in all three curves. To obtain a control value that would take into account any "drift" in the preparation over time, the pre-cyanide and recovery areas were averaged; the area during cyanide application was then expressed as a percent of this control value.

RESULTS

Experiments were done on a total of 33 slices from 17 guinea pigs. Four slices were exposed to 500 μM cyanide, 2 to 1000 μM, and 27 to concentrations in the range 5 - 200 μM as detailed in Table 1.

Application of cyanide at concentrations up to 500 μM and exposure times up to 45 min had no effect on the amplitude of the prevolley or the antidromic population spike. Of two slices exposed to 1000 μM cyanide, one showed no change in antidromic activation while the other showed a 40% decrease in antidromic population spike amplitude that occurred rapidly, was stable for the duration of cyanide application, and reversed as soon as cyanide was washed out.

Fig. 1 shows waveforms recorded in st. pyramidale of CA1 in response to orthodromic stimulation at fixed intensity before, during, and after application of 50 μM cyanide. During cyanide application the EPSP slope and the population spike amplitude are decreased, while the latency and width of the population spike are increased. These changes reversed rapidly and completely when the cyanide was washed out.
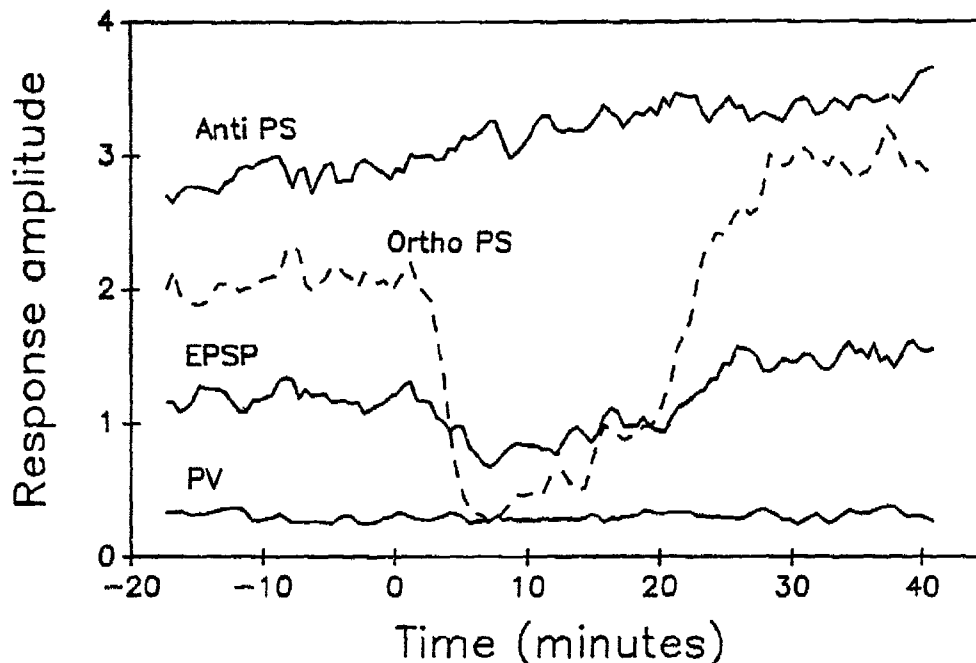
FIG. 2. Responses evoked in CA1 by fixed, submaximal stimulation pulses in a single slice that was exposed to 50 μM cyanide for 20 min starting at Time = 0. Anti PS, antidromic population spike. Ortho PS, orthodromic population spike. EPSP, focal excitatory postsynaptic potential. PV, presynaptic volley. The ordinate gives slope (in mV/mS) for EPSP and amplitude (in mV) for other measures.

Orthodromic synaptic transmission was suppressed or blocked by cyanide concentrations between 10 and 200 μM. A representative example is presented in Fig. 2, which shows the amplitudes of four response components, evoked by constant strength stimuli, over the course of an experiment in which 50 μM cyanide was applied for 20 min. The antidromic population spike and prevolley were unaffected by cyanide, while both the EPSP and orthodromic population spike were partially suppressed. Table 1 summarizes the depression of the orthodromic population spike caused by different cyanide concentrations.

I/O curves from one experiment in which 50 μM cyanide was applied are shown in Fig. 3, and pooled I/O data from all experiments are presented in Table 2. Analysis of I/O curves showed that there were two components to the suppression of overall synaptic transmission.

The curve relating EPSP to prevolley was depressed, indicating a decrease in transmitter release and/or a change in the response of the postsynaptic membrane to the transmitter. The curve relating population spike to EPSP was also depressed, indicating an increase in the action potential threshold of the pyramidal cells. The prevolley-stimulus curve was not affected. As the data in Table 2 indicate, the effects of cyanide on I/O curve components was dose-dependent.

In three experiments, slices were exposed to 200 μM cyanide while simultaneous recordings were made in CA1 and gyrus dentatus. In all cases, synaptic transmission was completely blocked in CA1 but only partially blocked in GD, as shown for one experiment in Fig. 4. This suggests that synapses in CA1 are more sensitive to the effects of cyanide than are synapses in GD.

DISCUSSION

These experiments demonstrate that, in the guinea pig hippocampal slice, acute exposure to micromolar cyanide concentrations inhibits or blocks excitatory synaptic transmission between Schaffer collateral-commissural fibers and CA1 pyramidal cells. This inhibition has two components, a decrease in EPSP generation and an decrease in pyramidal cell excitability.

Given the known effect of cyanide in blocking aerobic metabolism, it would not be unreasonable to expect that acute exposure to cyanide would result in a gradual neuronal depolarization as ATP stores are depleted and the Na+-K+ pump slows. Indeed, a decrease in EPSP amplitude, as seen in the present experi-

ments, could be caused by depolarization of either pre- or postsynaptic elements. Other aspects of the present results, however, mitigate the appeal of neuronal depolarization as a hypothetical mechanism. The observed decrease in pyramidal cell excitability is not consistent with pyramidal cell depolarization, and in fact argues that if any membrane potential change occurs it is more likely to be a hyperpolarization. Furthermore, the lack of change in the antidromic I/O curve indicates that there is no significant change in membrane potential, at least in the axons. Clearly, the question of cyanide-induced changes in membrane potential remains unsettled, and will require direct intracellular measurements for resolution.

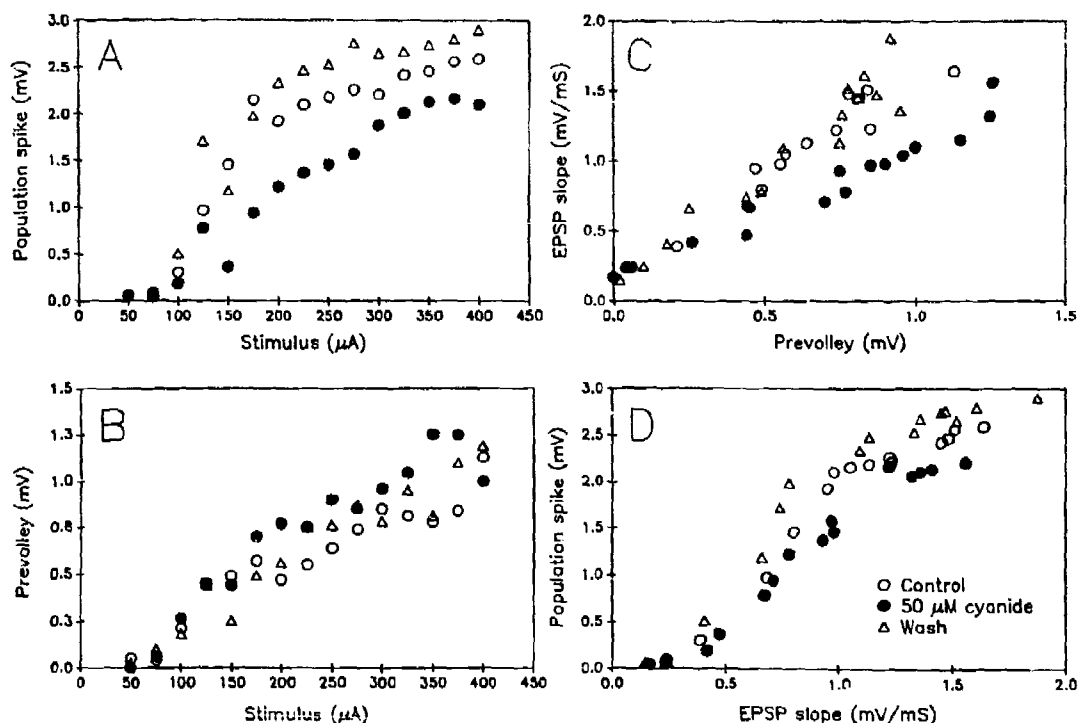If cyanide is acting by blocking aerobic metabolism and decreasing ATP levels, one

FIG. 3. I/O curves from one experiment in which 50 μM cyanide was applied to the slice for 20 min. Graph A is the overall I/O curve, showing a depression in the population spike evoked by a given stimulus intensity. Graphs B-D are the component I/O curves, showing that the stimulus-prevolley relationship was not affected (graph B), but that cyanide depressed both the prevolley-EPSP (graph C) and EPSP-population spike (graph D) relationships. For symbols, see legend in part D.
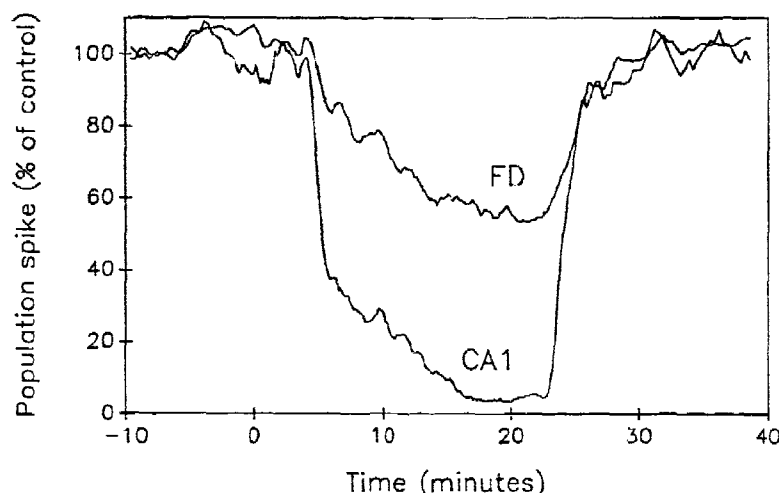
FIG. 4. The amplitude of orthodromic population spikes in CA1 and gyrus dentata of one slice recorded during 20 min exposure to 200μM cyanide (starting at Time = 0).

might expect its effects to resemble those of ouabain, which poisons the Na^+-K^+ pump. In at least one non-neural preparation, cyanide has been reported to "exactly mimic" the effects of ouabain (Rehwald and Lang, 1986). With the pump shut off, neurons would gradually depolarize and the membrane potential would move closer to threshold, causing a transient period of hyperexcitability followed by electrical failure. Such effects of ouabain have in fact been demonstrated in hippocampal slices by Schiff (1985), who reported that 10^5 M ouabain caused a rapid increase in population spike amplitude with no change in EPSP slope, followed by electrical failure. These effects of ouabian are in sharp contrast to the effects of micromolar cyanide, which causes an EPSP decrement without hyperexcitability or electrical failure. This further suggests that neuronal depolarization is not involved in the rapid effects of cyanide.

It is instructive to compare the effects of cyanide to the effects of hypoxia, a condition which cyanide intoxication might be expected to mimic in some respects. When deprived of oxygen, CA1 pyramidal cells exhibit a moderate, transient hyperpolarization accompanied by a decrease in excitability, followed by depolarization, hyperexcitability, and eventual electrical failure (Hansen *et al.*, 1982; Fujiwara *et al.*, 1987). These symptoms are quite different from the effects of cyanide observed in the present experiments. The differences between the effects of hypoxia and of cyanide argue against interpreting the effects of cyanide seen in these experiments as being due to a blockade of aerobic metabolism.

Another factor arguing that the present results are not secondary to cytochrome oxidase inhibition is the rapidity with which synaptic transmission recovered when cyanide was washed out. We have found no published evidence indicating that cyanide can dissociate from cytochrome oxidase with sufficient rapidity. In fact, the oxidized cyanide-cytochrome oxidase complex is considered to be "quite stable," particularly in the absence of reducing equivalents (Way, 1984).

Possible actions of cyanide in modifying calcium entry into neurons (Biscoe *et al.*, 1988; Duchen and Somjen, 1988) or modifying interstitial pH (Benabid *et al.*, 1987; Balestrino and Somjen, 1988) could also affect synaptic transmission, although these mechanisms have yet to be investigated in detail.

Our finding that CA1 and GD have different sensitivities to cyanide is quite interesting, particularly in light of the fact that these two regions also demonstrate a differential sensitivity to ischemia/hypoxia. CA1 pyramidal cells are more likely to degenerate following an ischemia episode than are dentate granule cells (Kirino and Sano, 1984; Spielmeyer, 1929). *In vitro*, synaptic transmission in CA1 is more sensitive to hypoxia than is synaptic transmission in GD (Aitken and Schiff, 1986; Balestrino *et al.*, in press).

In summary, there are two aspects of our data that support the possibility of a direct, non-metabolic effect of cyanide on the central nervous system: (1) The rapidity with which cyanide's effects reverse is not consistent with a reversal of cytochrome oxidase inhibition, and (2) Changes in synaptic function without concomitant changes in direct neural excitability are difficult to explain by a general compromising of neural oxidative metabolism. In the brains of animals killed by cyanide intoxication, cyanide concentrations reach levels similar to those used in these experiments (Ballantyne *et al.*, 1972; Ballantyne and Marrs, 1987), indicating that CNS effects could play a role in cyanide morbidity. Further work is needed, however, to determine whether a non-metabolic effect of cyanide on synaptic function is indeed at work.

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(GD), evoked by perforant path stimulation, were recorded simultaneously with CA1 responses during cyanide application. GD was found to be less sensitive to cyanide than CA1. All cyanide effects reversed rapidly and completely upon washout. These findings suggest that cyanide has a direct effect on neurons not mediated by its inhibition of metabolism. © 1989 Intox Press, Inc.