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EFFECTS OF CYANIDE *IN VITRO* ON THE ACTIVITY OF MONOAMINE OXIDASE IN STRIATAL TISSUE FROM RAT AND PIG

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Abstract—We have shown previously in the rat that lethal, acute cyanide intoxication dramatically decreased the levels of dopamine (DA) in the striatum, while the synthesis of DA was increased. The main brain metabolite of DA, homovanillic acid, was also diminished. However, the levels of the oxidatively deaminated metabolite of DA, 3,4-dihydroxyphenylacetic acid, were not significantly changed. In order to elucidate further these findings we examined the effects *in vitro* of sodium cyanide on rat and pig brain monoamine oxidase (MAO; EC 1.4.3.4). The MAO activity was measured radiochemically using [^{14}C]5-hydroxytryptamine (5-HT; 100 μM), [^{14}C]phenethylamine (PEA; 20 μM) and [^{14}C]DA (100 μM) as substrates. The amounts of cyanide added were comparable to those tissue concentrations of cyanide usually considered to be fatal in rats. The effect of cyanide on MAO was immediate. In rat, as well as pig, striatal tissue we found that cyanide produced a dose-dependent increase in the activity of MAO-A (as measured with 5-HT), but not MAO-B (as measured with PEA). The change in MAO activity was also seen with DA as substrate (MAO-A and -B). Kinetic constants, K_m and V_{max}, were determined. In both rat and pig striatum the V_{max} values for 5-HT were significantly increased, but the values for PEA were not affected. A significant decrease in the K_m value for PEA was, however, found in the presence of high concentrations of cyanide.

Acute, lethal cyanide poisoning is consistently accompanied by high concentrations of cyanide in the brain. There are also several symptoms and signs indicating that the brain is a major target site for cyanide [1, 2]. The inhibition of the enzyme cytochrome oxidase is thought to be the main molecular basis of these effects. This inhibitory effect causes impaired oxygen utilization in all cells affected, resulting in severe metabolic acidosis and inhibited production of energy [3, 4]. However, in acute lethal cyanide intoxication interactions with other oxidative enzymatic systems can also be expected. In fact, many of these enzymes seem to be even more sensitive to cyanide than cytochrome oxidases [5]. An increased tyrosine hydroxylase activity *in vivo* has been shown after cyanide treatment [6].

Monoamine oxidase (MAO§; EC 1.4.3.4) is an enzyme considered to have an important role in the regulation of the levels of biogenic amines in the brain and peripheral tissues. The enzyme exists in two forms, MAO-A and MAO-B, which differ in sensitivity to inhibitors and in substrate specificity. Thus, the A-form is particularly sensitive to inhibition (in the nanomolar range) by clorgyline and will preferentially deaminate substrates such as 5-hydroxytryptamine (serotonin; 5-HT), noradrenaline and partially dopamine (DA). The B-form is inhibited only by very high concentrations (in the micromolar range) of clorgyline and preferentially deaminates β-phenethylamine (PEA) but also partially DA. Both forms of MAO are found in most mammalian tissues, where they have been looked for. However, a wide species variation exists in their relative activities and regional distribution. Thus, the rat brain displays more MAO-A activity and human and pig brain more MAO-B activity [7, 8].

It has been shown previously in rats that there is a dose-dependent decrease in the concentration of striatal DA, as well as in the level of its main brain metabolite homovanillic acid (HVA), within 60 sec of injection of sodium cyanide (NaCN; 5–20 mg/kg i.p.). However, the acid metabolite 3,4-dihydroxyphenylacetic acid (DOPAC), which represents intraneuronal metabolism of DA [9], was not changed [10].

To our knowledge there are only a few reports concerning the effect of cyanide on brain MAO. Hall and Logan [11], for example, could not find any effect of potassium cyanide (KCN; 1 mM) on rat brain MAO, and in single nerve cell bodies isolated from the locus coeruleus of rats Sket and Pavlin [12] found no effect of KCN (1 and 10 mM). In both cases, the MAO activity was estimated by measuring the oxygen consumption with tyramine as substrate (i.e. both MAO-A and -B activity was measured).

The important role of the enzyme MAO in the regulation of the circulating levels of a number of monoamines and the above-mentioned effects of cyanide on the levels and metabolism of DA in the rat prompted us to perform this study. Thus, the

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§ Abbreviations: MAO, monoamine oxidase; 5-HT, 5-hydroxytryptamine (serotonin); PEA, phenethylamine; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid.

aim was to elucidate, in an *in vitro* design, the effect of NaCN on the activity of MAO in striatal tissue from rat and pig. One reason for choosing the pig was the similarities between the pig and the human brain with regard to the dominance of MAO-B over MAO-A.

The concentrations of cyanide needed to produce neuronal death *in vitro* have been shown to be 10–100 times greater than those needed to produce neuronal death *in vivo* [13]. Concentrations above 100 μM, as used in our experiments, are similar to those known to produce neuronal death *in vivo* [14]. Part of this study has been reported preliminarily [15].

MATERIALS AND METHODS

Chemicals. NaCN was obtained from Merck (Darmstadt, Germany). [^{14}C]5-HT ([^{14}C]5-hydroxytryptamine binoxalate, 56.7 mCi/mmol), [^{14}C]PEA ([^{14}C]2-phenethylamine hydrochloride, 55.5 mCi/mmol) and Econofluor were obtained from NEN (Boston, MA, U.S.A.). [^{14}C]DA (3,4-[8-^{14}C]dihydroxyphenylethylamine hydrobromide, 56.0 mCi/mmol) was purchased from Amersham (U.K.). All other chemicals used were *pro analysi* or of higher purity. Solutions were made up just before use.

Animals. Male, Sprague–Dawley rats (N = 9; body wt 177–213 g), from ALAB, now Bantin and Kingman International (Sollentuna, Sweden) have been used in all experiments. They were killed by decapitation and the brains were quickly removed and placed on ice-cold Petri dishes for dissection of the striata.

Brains from pigs (N = 6; body wt 70–80 kg) were obtained from the local slaughter house. They were chilled on ice and rapidly transported to the laboratory for further dissection. All these procedures were completed within 30 min.

The experiments have been approved by the Regional Research Ethical Committee according to national laws (SFS 1988:539, LSFS 1989:41).

Measurement of the MAO activity. The striata were homogenized (six strokes at 600 rpm) using a Potter–Elvehjem homogenizer equipped with a teflon pestle in 9 vol. of ice-cold 0.32 M sucrose and then diluted 1/10 in water. The MAO activity was measured radiochemically using [^{14}C]5-HT (100 μM), [^{14}C]PEA (20 μM) and [^{14}C]DA (100 μM) as substrates. The reaction media contained 20 μL of tissue homogenates and 20 μL NaCN (12.5, 25, 50, 100, 200, 400, 800 μM) dissolved in 10 μM K-phosphate buffer, pH 7.4 with 0.2 mg/mL ascorbate as an antioxidant. The final assay volumes in the test tubes were 100 μL. The reactions were started by addition of the labelled substrates and continued for 4 min (PEA) or 20 min (DA and 5-HT) at 37° in a shaking water bath in an atmosphere of air. At the end of the incubation period the reactions were stopped by addition of 3 M HCl and cooling the tubes on ice. Blank values were obtained by adding the HCl prior to the incubations. Deaminated products were extracted into 6 mL toluene–etylacetate (1:1, v/v) saturated with water and the radioactivity was counted in 10 mL of Econofluor. Values for the extraction efficiencies were used to allow activities to be expressed in absolute terms [16]. When the effects of different preincubation times on MAO activity were studied, NaCN (50 μM, 400 μM) was added to the homogenate 5, 10, 15, 20, 30, 45 and 60 min before adding the substrates.

With 5-HT (6.25–100 μM) and PEA (2.5–40 μM) and in the presence or absence of 50 or 800 μM cyanide the kinetic constants, K_m and V_{max}, were determined in the assay procedure, as described above. Results were plotted as initial velocities against initial velocity/substrate concentrations (v against v/s; Eadie–Hofstee plot) and the constants were determined by linear regression analysis. In all cases, the correlation coefficients of regression lines were higher than 0.96. Protein concentrations were assayed by the method of Markwell *et al.* [17] with bovine serum albumin as standard and the activity of the enzymes was expressed as nmol/mg protein/min.

Statistics. The two-tailed Student's t-test and ANOVA (K_m and V_{max}) were employed for significance testing. $P \leq 0.01$ was chosen as level of significance.

RESULTS

We found it important to examine whether preincubation with cyanide for different time periods would affect the MAO activity. However, the effect of cyanide, when tested in rat brain, was found to be immediate with no effect of time (Table 1). Preincubation was considered unnecessary and in the following experiments we added cyanide together with the substrates. Figures 1, 2 and 3 show the effect of increasing concentrations of cyanide on the oxidative deamination of 5-HT (100 μM), PEA (20 μM) and DA (100 μM) in the striatal homogenates. In both rat and pig, the oxidative deamination of 5-HT (Fig. 1) and DA (Fig. 2) increased in a significant dose-dependent manner. The oxidative deamination of PEA was, however, not significantly changed (Fig. 3).

In the absence or presence of two different concentrations of cyanide (50 and 800 μM) the dependence of the MAO activities on the concentration of 5-HT (6.25–100 μM) and PEA (2.5–40 μM) was determined. The K_m and V_{max} values derived from these experiments, after transformation of the data, are shown in Tables 2 (rat brain) and 3 (pig brain).

When homogenates from rat brains were exposed to cyanide at 800 μM the V_{max} value for 5-HT was significantly ($P = 0.0065$) increased (from 1.7 to about 2.1 nmol/mg protein/min = 23%). No significant effect on the K_m values was found with 5-HT as substrate. The V_{max} value for PEA was not affected, but there was a significant ($P = 0.0058$) decrease in the K_m value in the presence of 800 μM cyanide.

In pig striatal tissue homogenates (Table 3) cyanide at 800 μM produced a slight but significant ($P > 0.0001$) increase in the V_{max} value for 5-HT (from 1.0 to 1.3 nmol/mg protein/min = 30%). However, the K_m values were not significantly affected by the two concentrations of cyanide used. The V_{max} values for PEA were not significantly

Table 1. Effect of different preincubation times (0 and 60 min) with sodium cyanide (400 μM) on rat brain MAO activity

Substrate	Time (min)	Activity (nmol/mg protein/min)	% of controls
PEA	0	1.14 ± 0.04	101.1
PEA	60	1.14 ± 0.03	99.6
5-HT	0	1.58 ± 0.04	112.1
5-HT	60	1.65 ± 0.06	118.6
DA	0	0.32 ± 0.002	113.3
DA	60	0.33 ± 0.007	117.1

The activities are given as nmol/mg protein/min (mean ± SD; N = 3).

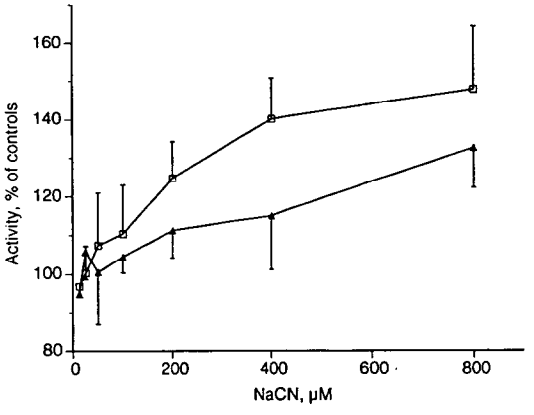

Fig. 1. The effects of sodium cyanide on the deamination of 5-HT after incubation with different doses. (□) Rats, (▲) pigs. The results are expressed as % of controls. The control values were 1.40 ± 0.12 and 0.73 ± 0.03 nmol/mg protein/min for rat and pig, respectively. (Mean ± SD; N = 9, rat and N = 6, pig.) $P < 0.01$ for 200–800 μM NaCN.

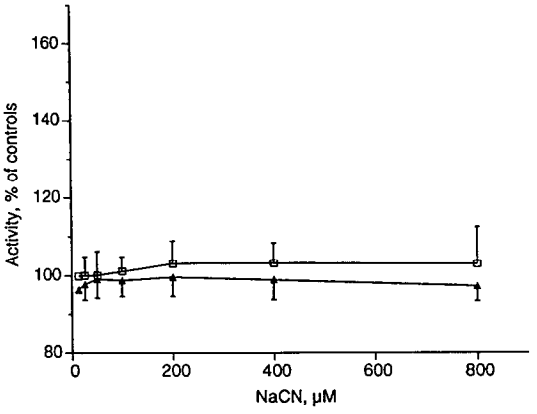

Fig. 3. The effects of sodium cyanide on the deamination of PEA after incubation with different doses. (□) Rats, (▲) pigs. The results are expressed as % of controls. The control values were 1.16 ± 0.12 and 3.23 ± 0.15 nmol/mg protein/min for rat and pig, respectively. (Mean ± SD; N = 9, rat and N = 6, pig.)

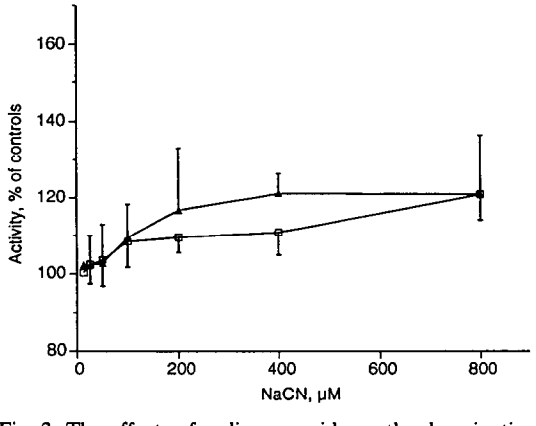

Fig. 2. The effects of sodium cyanide on the deamination of DA after incubation with different doses. (□) Rats, (▲) pigs. The results are expressed as % of controls. The control values were 0.28 ± 0.04 and 0.76 ± 0.04 nmol/mg protein/min for rat and pig, respectively. (Mean ± SD; N = 9, rat and N = 6, pig.) $P < 0.01$ for 400–800 μM NaCN.

different, but at 800 μM cyanide the apparent K_m value for PEA was significantly ($P > 0.001$) decreased.

DISCUSSION

To our knowledge, there are no studies reported concerning effects of cyanide on the oxidative deamination of 5-HT and DA in rat or pig brain. *In vitro* 5-HT is mainly a substrate of MAO-A. This is the case in the rat as well as in the pig brain, while DA is a substrate for both forms of MAO. The influence of cyanide on the oxidative deamination of tyramine has been studied mostly in rat liver but also in the locus coeruleus [11, 12, 18–20]. Tyramine is a substrate for both MAO-A and -B. Studies have also been performed with benzylamine and PEA [21, 22], which are substrates for MAO-B. We now report that cyanide dose-dependently increases the oxidative deamination of 5-HT and DA in pig and rat striatal tissue homogenates. Although there was a dose-dependent increase in the MAO activity, when DA was used as a substrate the increase was smaller than that observed with 5-HT as a substrate.

Table 2. Kinetic data (from rats) estimated from an Eadie–Hofstee plot using linear regression

NaCN (μM)	MAO-A K_m (μM)	MAO-A V_{max} (nmol/mg protein/min)	MAO-B K_m (μM)	MAO-B V_{max} (nmol/mg protein/min)
0	27.3 ± 2.2	1.7 ± 0.1	3.3 ± 0.3	1.6 ± 0.1
50	26.8 ± 3.2	1.8 ± 0.2	3.2 ± 0.4	1.7 ± 0.1
800	24.2 ± 2.6	2.1 ± 0.2*	2.8 ± 0.3*	1.7 ± 0.2

ANOVA was used for statistical calculation (mean ± SD; N = 9). * $P < 0.01$.

Table 3. Kinetic data (from pigs) estimated from an Eadie–Hofstee plot using linear regression

NaCN (μM)	MAO-A K_m (μM)	MAO-A V_{max} (nmol/mg protein/min)	MAO-B K_m (μM)	MAO-B V_{max} (nmol/mg protein/min)
0	60.4 ± 21.7	1.0 ± 0.2	2.3 ± 0.5	2.8 ± 0.7
50	58.6 ± 21.5	1.1 ± 0.5	2.1 ± 0.6	2.7 ± 0.7
800	58.6 ± 19.4	1.3 ± 0.2*	1.7 ± 0.6*	2.6 ± 0.6

ANOVA was used for statistical calculation (mean ± SD; N = 14). * $P < 0.001$.

This probably reflects the fact that DA is oxidatively deaminated by both MAO-A and -B. Interestingly, the oxidative deamination of PEA was not significantly changed. Thus, when the enzyme preparations were subjected to increasing concentrations of cyanide there was an increase in the ratio of MAO-A to MAO-B (an increase in MAO-A activity with MAO-B activity apparently unaffected). The difference in sensitivity to cyanide between MAO-A and -B cannot be a consequence of the difference in incubation time as seen in Table 1.

In mammalian [18] and guinea-pig [19, 20] liver cyanide (1 mM) has been reported not to change the MAO activity. It has also been shown that cyanide does not affect MAO-B activity in rat liver [20], which is in agreement with our results from pig and rat striatal tissue. In contrast, MAO-B has also been shown to be reversibly inhibited in rat liver [22]. However, there may certainly be tissue as well as species specificities with regard to the effect of high concentrations of cyanide. In single nerve cell bodies isolated from the locus coeruleus of the rat no effect of KCN was found [12]. Within nervous tissue acute neurotoxicity from cyanide has been associated with accumulation of calcium [23, 24]. Studies on rat liver mitochondria have provided evidence that translocations of calcium ions can trigger a decrease in MAO activity [25]. Thus, the data concerning the effect of cyanide on MAO are conflicting and partly at variance with our results. One explanation for this could be that we have specifically measured the activity of MAO-A (as estimated with 5-HT). Another explanation could be differences in the enzyme preparations used. Furthermore, when assaying the MAO activity, the consumption of oxygen has been used in some experiments [11, 12, 18–20]. It is known that high cyanide concentrations, as used in these studies, can produce a large decrease in O_2 uptake in isolated aortic smooth muscle preparations [26], while low NaCN concentrations can increase the brain slice O_2 consumption [27]. As oxygen is necessary for oxidative deamination it is possible that the use of cyanide in the oxygen consumption method could seriously interfere with the measurements.

In both rat and pig the differences in activity at the high concentrations of cyanide (800 μM) appeared to be due entirely to differences in the V_{max} values of MAO with 5-HT as a substrate. There was no difference in the affinity (K_m) of the substrate. Unexpectedly, in both species there was a slight increase in the affinity of PEA for MAO with no concomitant change in the V_{max} value, when cyanide was used at a concentration of 800 μM.

The most important step in the elimination of DA released from presynaptic terminals by normal nerve activity is the re-uptake mechanism and the subsequent metabolism by intraneuronal MAO [28]. Any alterations in the levels of DOPAC may thus be seen as a function of re-uptake of released DA. Changes in the levels of HVA could be interpreted as reflecting either a change in available DA or in the MAO activity. It has earlier been shown in rats that administration of low doses (2.5 mg/kg; i.p.) and high, lethal doses (5–20 mg/kg; i.p.) of cyanide induced different effects on the levels of DA in the striatum [6, 10]. After lethal doses of cyanide there was a significant, dose-dependent decrease both in the levels of DA and its main brain metabolite, HVA. However, no significant change in DOPAC was seen [10]. Certainly, the relationship between the increased activity of MAO-A found in this study and the effect of cyanide on DA transmission and metabolism [6, 10] needs to be further elucidated. By interference with Ca^{2+} and/or ATP production

cyanide might affect both the granular uptake and the release of DA. Furthermore, a change in the release of DA could affect the activation of presynaptic autoreceptors and/or postsynaptic receptors. Any effect on the negative feed-back system will also affect the synthesis of DA [29] and result in changed levels of free DA within the DA neurons. The ATP-dependent granular uptake of DA could be impaired or blocked in rats treated with high doses of cyanide. The interference with the granular uptake could affect the intraneuronal oxidative deamination of DA. This could be a possible explanation for the observed unchanged striatal DOPAC level despite lowered DA and HVA levels in cyanide-treated rats. However, when incubating a tissue homogenate with a relatively high concentration of the substrate (as used by us), one gets no information about the enzyme activity within the intact neurons. Under such conditions, when the neuronal amine transport processes probably do not work as in intact neurons, the extraneuronal MAO dominates.

Severe cyanide intoxication in man has been shown to produce lesions in the basal ganglia and symptoms similar to Parkinson's disease [30–32]. A reactive gliosis in Parkinson's disease is one of the few clinical conditions where increased oxidative deamination has been observed [33, 34].

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