Pergamon

PII: S0306-4522(97)00454-5

Neuroscience Vol. 83, No. 3, pp. 791–798, 1998

0306–4522/98 $19.00+0.00

LOW ACTIVITY OF KEY PHOSPHOLIPID CATABOLIC AND ANABOLIC ENZYMES IN HUMAN SUBSTANTIA NIGRA: POSSIBLE IMPLICATIONS FOR PARKINSON'S DISEASE

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Abstract—To determine whether increased oxidative stress in substantia nigra of patients with idiopathic Parkinson's disease might be related to decreased ability of nigral cells to detoxify oxidized membrane phospholipids, we compared levels of the major phospholipid metabolizing enzymes in autopsied substantia nigra with those in non-nigral ($n=11$) brain areas of the normal human brain. Whereas most enzymes possessed a relatively homogeneous distribution, the activity of the major phospholipid catabolizing enzyme phospholipase A_2, assayed in the presence of calcium ions, varied amongst different regions, with substantia nigra possessing the lowest activity. Similarly, calcium-independent phospholipase A_2 activity, although possessing a relatively homogeneous regional distribution, was also low in the substantia nigra. This, coupled with low activity of phosphoethanolamine- and phosphocholine-cytidylyltransferases, major regulatory enzymes of phospholipid synthesis, in this brain region, suggest that the rate of phospholipid turnover is low in the substantia nigra.

Low activity of key phospholipid catabolic and anabolic enzymes in human substantia nigra might result in reduced ability to repair oxidative membrane damage, as may occur in Parkinson's disease. © 1998 IBRO. Published by Elsevier Science Ltd.

Key words: phospholipase A_2, phosphocholine cytidylyltransferase, phosphoethanolamine cytidylyltransferase, substantia nigra, Parkinson's disease, oxidative stress.

Idiopathic Parkinson's disease (PD) is characterized by progressive degeneration of neurons in the substantia nigra. Although the neurodegenerative mechanism is unknown, much evidence implicates the involvement of free radicals causing oxidative damage to cellular components.[22] Thus, levels of cholesterol hydroperoxides[7] and DNA oxidation products[14] are increased in the substantia nigra of patients with PD, as is the activity of mitochondrial Mn-superoxide dismutase,[20] whereas levels of reduced glutathione, an anti-oxidant, are decreased.[23] Such changes are consistent with elevated rates of free radical-mediated damage in PD.

A major cellular target for free radical damage is the polyunsaturated fatty acid (PUFA) esterified to membrane phospholipid molecules. In PD, levels of PUFAs are reduced in the substantia nigra, whereas the abundance of malondialdehyde, a product of lipid peroxidation, is increased.[6] Removal of toxic lipid peroxides from the membrane appears to play an important part in the detoxification of damaged PUFAs.[28] The enzymes responsible for this process are phospholipases A_2 (PLA_2), a family of enzymes including both calcium-stimulated and calcium-independent forms,[16] which catalyse the hydrolytic removal of fatty acids from the *sn*-2 position of the phospholipid molecule (the position at which most PUFAs are esterified) to form free fatty acid and lysophospholipid. Thus, several reports have demonstrated that PLA_2 activity is required to release peroxidized fatty acids for subsequent detoxification by glutathione peroxidase, which reduces fatty acid hydroperoxides to less toxic hydroxy fatty acids.[9,25] Failure to reduce lipid hydroperoxides will allow their reaction with metal ions to form alkoxy and peroxy radicals which can oxidize neighbouring PUFAs and proteins.[8] In addition, the hydroperoxides can decay, through a series of complex reactions, into hydrocarbons, for example pentane, and aldehydes, such as 4-hydroxy-2,3-*trans*-nonenal, which damage proteins via reaction with amino and sulphydryl groups.[4] Importantly, PLA_2 displays a preference for phospholipids containing free radical-damaged PUFAs over intact molecules, again suggesting that PLA_2 plays an important role in the cellular response to free radical damage.[1,12,21,26]

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Abbreviations: EDTA, ethylenediaminetetra-acetate; EGTA, ethyleneglycolbis(aminoethylether)tetra-acetate; GPCPD, glycerophosphocholine phosphodiesterase; HEPES, *N*-2-hydroxyethylpiperazine-*N'*-2-ethane-sulphonic acid; PC, phosphatidylcholine; PCCT, phosphocholine cytidylyltransferase; PD, Parkinson's disease; PE, phosphatidylethanolamine; PECT, phosphoethanolamine cytidylyltransferase; PLA_2, phospholipase A_2; PUFA, polyunsaturated fatty acid.

Thus PLA_2, by means of its key role in phospholipid catabolism, may play an important role in membrane restoration following oxidative damage.

Although PLA_2 initiates the turnover of phospholipid fatty acid residues, many other enzymes have an important role in this metabolic system. Thus, the toxic[29] lysophospholipid formed by the action of PLA_2 is either re-acylated by lysophospholipid:acyl CoA acyltransferase (acyltransferase), or further hydrolysed by lysophospholipase to produce a glycerophosphodiester such as glycerophocholine.[15] Subsequently, the glycerophosphodiester is hydrolysed by a diesterase such as glycerophosphocholine-phosphodiesterase (GPCPD)[19] to produce glycerol and phosphomonoester e.g., phosphocholine, the latter being further broken down by alkaline phosphatase to release the head group moeity of the original phospholipid molecule.

Once phospholipids have been degraded by this means, the initial step in the resynthesis of phosphatidylcholine (PC) and phosphatidylethanolamine (PE), the two quantitatively major phospholipid classes, is phosphorylation of choline and ethanolamine to form phosphocholine and phosphoethanolamine, reactions catalysed by choline kinase and ethanolamine kinase, respectively. Phosphocholine and phosphoethanolamine are subsequently converted to cytidinediphosphocholine and cytidinediphosphoethanolamine, reactions catalysed by phosphocholine cytidylyltransferase (PCCT) and phosphoethanolamine cytidylyltransferase (PECT). Finally, the cytidinediphospho-derivatives react with diacylglycerol or 1-alkyl-2-acyl glycerol to form either PC or PE, as catalysed by choline phosphotransferase or ethanolamine phosphotransferase.

Since PLA_2 activity is required for glutathione peroxidase to detoxify oxidised PUFAs, as well as removing polar, membrane-disruptive hydroxy fatty acids from the membrane,[28] low rates of PLA_2-initiated phospholipid turnover could slow the removal of damaged phospholipid molecules,[3] thereby increasing the cell's sensitivity to free radical attack, and to the neurodegenerative process in PD. We address this possibility in the present investigation, in which the activity of PLA_2, and that of other enzymes of phospholipid metabolism, are determined in nigral vs non-nigral regions of the normal human brain.

EXPERIMENTAL PROCEDURES

Autopsied human brain tissue

Temporal, occipital, frontal and parietal cortices (Brodmann areas 21, 17, 10, 7b, respectively), cerebellar cortex, hippocampus, caudate nucleus, putamen, substantia nigra, medial dorsal thalamus, pulvinar, and subcortical white matter (taken rostral to the caudate nucleus) were dissected from the autopsied brains of 10 neurologically and neuropsychiatrically normal subjects [age 61 ± 5 years (mean ± S.E.M.); *post mortem* interval 10 ± 1 h]. Due to tissue limitations, a subset of seven cases was analysed for the thalamic areas. However, the age (57 ± 3 years) and *post mortem* interval (11 ± 1 h) of these seven cases was not significantly different from the complete group of 10 cases ($P > 0.5$ by two-tailed Student's *t*-test). For the characterization of choline phosphotransferase, temporal cortex (Brodmann area 21) from the brains of three neurologically and neuropsychiatrically normal subjects aged 51 ± 8 years, having a *post mortem* interval of 8 ± 1 h, were used.

Enzyme assays

Tissue to be used in enzyme assays was first disrupted by probe sonication in five volumes of 50 mM HEPES, 1 mM EDTA and 1 mM EGTA as previously described.[15] As indicated in the text, some experiments also employed 1 M potassium chloride extracts of the particulate fraction (100,000 g_{av} pellet) as described.[16] Choline phosphotransferase activity was assayed as described[4] with some modifications to optimize assay conditions for the human brain enzyme which had not been characterized previously. In preliminary experiments, using homogenate preparations of autopsied human temporal cortex, choline phosphotransferase activity was found to possess a pH optimum of 7.5, falling to approximately 50% of activity recorded at pH 7.5 at pH 6.5 and pH 8.5 (data not shown). CDP-choline and 1,2-dioleoyl-*sn*-glycerol possessed K_m values of 17 ± 3 μM (mean ± S.E.M.; $n = 3$) and 1.8 ± 0.2 mM, respectively, for choline phosphotransferase (data not shown). Under the V_{max} conditions routinely employed, the rate of phosphatidylcholine formation was linear with respect to time for at least 1 h, and with respect to protein up to at least 300 μg homogenate protein. Choline phosphotransferase was routinely assayed by incubating 200 μg of homogenate protein at 37°C for 45 min along with 10 mM 1,2-dioleoyl-*sn*-glycerol, 100 μM cytidine diphospho[*methyl*-^{14}C]choline (15 Ci/mol), 10 mM magnesium chloride, and 100 mM HEPES, pH 7.5 in a final volume of 50 μl. The reaction was terminated by the addition of 500 μl chloroform/methanol (1:2 v/v) followed by the sequential addition of 300 μl chloroform and 500 μl water. The tubes were vortexed for 1 min, centrifuged and the aqueous phase removed. The lower phase was then washed twice with 1 ml of chloroform/methanol/water (3:48:47 v/v/v), and radioactivity in the lower phase quantified by liquid scintillation counting. In preliminary experiments the lower phase was dried by vacuum centrifugation, resuspended in a small volume of choloform/methanol (1:2 v/v), and analysed by thin layer chromatography on silica gel developed in either chloroform/methanol/water (65:35:4 v/v/v) or chloroform/methanol/acetic acid/water (75:45:8:2 v/v/v/v).[15] Using either solvent, the radioactive product migrated as a single spot, as assessed by autoradiography, co-migrating with that of an authentic phosphatidylcholine standard.

Assays for PLA_2 (calcium-stimulated and calcium-independent), lysophospholipase, acyltransferase, GPCPD, choline kinase, ethanolamine kinase, PCCT and PECT were carried out as described previously.[15–19] The assay conditions, altered slightly for use in tissue homogenates rather than subcellular fractions, are summarized in Table 1. Assay of PLA_2 activity in particulate salt extracts of human brain was carried out as described previously.[16]

RESULTS

Phospholipase A_2

As assessed by one-way ANOVA, calcium-stimulated PLA_2 possessed a heterogeneous distribution in human brain which varied over an approximately three-fold range, with activity being highest in cortical areas, lower in subcortical white matter, thalamus, and cerebellum, and lowest in

Table 1. Summary of assay characteristics

Enzyme	Substrate and ionic requirements	Product	pH	Protein (μg)	Time (min)
Calcium-stimulated PLA_2	50 μM 1-palmitoyl, 2-[^{14}C]-arachidonyl PE, 1 mM calcium chloride	Fatty acid	8.5	20	45
Calcium-independent PLA_2	50 μM 1-palmitoyl, 2-[^{14}C]-arachidonyl PE, 1 mM calcium chloride	Fatty acid	7.0	20	45
Lysophospholipase	50 μM 1-[^{14}C]-palmitoyl lyso PC	Fatty acid	8.0	2	45
Acyltransferase	10 mM 1-palmitoyl lyso PC, 100 μM [1-^{14}C]-arachidonyl PC	Phosphatidylcholine	6.0	20	5
GPCPD	0.5 mM glycerol-3-phospho-[*methyl*-1-^{3}H]-choline, 5 mM zinc acetate	Phosphocholine	10.5	200	45
Choline kinase	2 mM [^{14}C]-choline, 10 mM ATP	Phosphocholine	8.0	200	45
Ethanolamine kinase	0.5 mM [^{14}C]-ethanolamine, 10 mM ATP	Phosphoethanolamine	8.0	100	45
PCCT	2 mM [^{14}C]-phosphocholine, 10 mM ATP	CDP-choline	7.5	200	60
PECT	0.5 mM [^{3}H]-phosphoethanolamine, 10 mM ATP	CDP-ethanolamine	7.5	200	60

Enzymes are abbreviated as defined in the text.

the substantia nigra (Fig. 1A, Table 2). Calcium-independent PLA_2 activity was also lowest in the substantia nigra, but did not possess significant heterogeneity amongst the other brain regions (Fig. 1B, Table 2). Neither calcium-stimulated nor calcium-independent PLA_2 activities, or the activities of the other enzymes studied, were significantly ($P>0.05$) correlated with the time between death and autopsy in any brain region examined (Fig. 2), making it unlikely that low nigral PLA_2 is an artefact of the autopsy process. We next investigated whether low nigral PLA_2 activity was observable using PC, as opposed to PE, as substrate. Since the activity of PLA_2 catalysed hydrolysis of PC is too low to be reliably measured using homogenate preparations, we employed potassium chloride extracts of the particulate cell fraction in which the specific activity of calcium-stimulated, but not calcium-independent, PLA_2 is higher.[14] Calcium-stimulated PLA_2 activity in salt extracts of the substantia nigra was approximately 40% of that in the temporal cortex of four randomly chosen subjects when using either PE or PC as substrate (Table 3). To address the possibility that low PLA_2 activity in the substantia nigra might be due to the presence of an endogenous inhibitor, nigral homogenates were included in the assay of PLA_2 derived from other brain regions. Nigral homogenates, obtained from five subjects chosen randomly from the set of 10, were not capable of inhibiting either the calcium-stimulated or calcium-independent PLA_2 activities of human temporal cortex, hippocampus or cerebellum (Table 4).

Lysophospholipase, acyltransferase and glycerophosphocholine phosphodiesterase

With the exception of low activity in subcortical white matter, lysophospholipase activity was homogeneously distributed between the areas examined (Fig. 1C, Table 2). Acyltransferase activity was similar in all regions analysed with the exception of the cerebellum, which possessed approximately two-fold higher activity than the other brain areas (Fig. 1D, Table 2). Activity of GPCPD was strikingly high in subcortical white matter (approximately five- to 10-fold higher than other brain areas), and lowest in the temporal cortex, cerebellum and striatum (Fig. 1E, Table 2).

Enzymes of de novo *synthesis*

Choline phosphotransferase activity was homogeneously distributed amongst all of the cortical and subcortical regions examined (Fig. 3E, Table 2). Choline and ethanolamine kinase activities were homogeneously distributed in the gray matter structures examined (Fig. 3A,B, Table 2), although lower activities were observed in subcortical white matter. PCCT activity was similar in the cortex, caudate, putamen and cerebellum, but was somewhat lower in the thalamic areas, white matter and substantia nigra (Fig. 3C, Table 2). Of all the synthetic pathway enzymes studied, PECT possessed the most heterogeneous regional distribution (Fig. 3D, Table 2), with lowest activity in the substantia nigra (approximately one-third of that in other brain regions), and, in contrast to PCCT, highest in white matter.

DISCUSSION

Our major finding was the prominent heterogeneity of calcium-stimulated PLA_2 activity amongst different regions of the human brain, in marked contrast to the generally homogeneous distribution of most of the other examined enzymes of phospholipid metabolism.

Enzymes possessing similar activity in the substantia nigra to that in other brain regions

Our finding that the majority of the phospholipid metabolizing enzymes examined possess similar activity in different areas of the human brain is not surprising given the ubiquitous need for synthesis and renewal of phospholipid molecules. However,

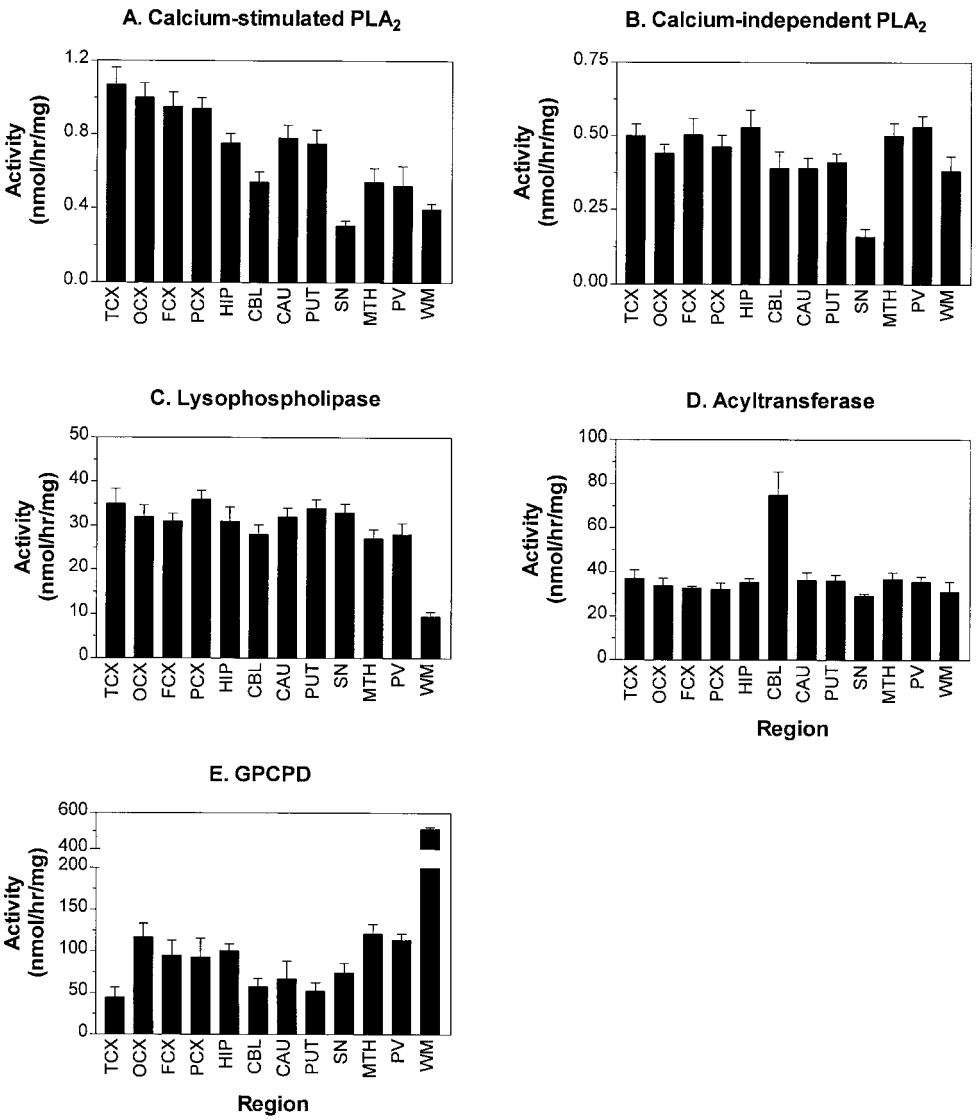

Fig. 1. Regional distribution of phospholipid metabolizing enzymes in the autopsied human brain. Values shown are mean activity of 10 subjects except for MTH and PV when seven subjects were used. Bars indicate the S.E.M. Note break in axis in panel E (GPCPD). TCX, temporal cortex; OCX, occipital cortex; FCX, frontal cortex; PCX, parietal cortex; HIP, hippocampus; CBL, cerebellar cortex; CAU, caudate; PUT, putamen; SN, substantia nigra; MTH, medial thalamus; PV, pulvinar; WM, subcortical white matter.

there were several exceptions. For example, GPCPD activity was markedly (approximately five- to 10-fold) higher in white matter than in other brain structures, an observation in keeping with the fact that glycerophosphodiester levels are also highest in white matter.[13] Although the coincident occurrence of both high glycerophosphodiester and GPCPD activity in white matter could be explained by similarly high rates of glycerophosphodiester formation from membrane phospholipids, our observation that both PLA_2 and lysophospholipase possess relatively low activity in white matter makes this explanation unlikely. However, we cannot rule out the possibility that high white matter glycerophosphodiester levels are due to their formation via PLA_1, or by an additional, as yet uncharacterized, synthetic route.

PECT activity was also higher in white compared to gray matter structures, contrasting with PCCT activity which was relatively low in white matter. This distribution correlates well with the relative abundance of PE and PC in different brain regions, with PE being the major phospholipid in white matter, whereas PC predominates in gray matter.[24] Such a relationship provides further evidence for the hypothesis that PCCT and PECT are the rate-limiting steps of PC and PE synthesis[10] in brain.

We also observed that acyltransferase activity, while possessing a generally homogeneous

Table 2. ANOVA analysis of the regional distribution of phospholipid metabolizing enzymes in human brain

Enzyme	All regions		Excluding white matter[a], substantia nigra[b] or cerebellum[c]	
	F-ratio	*P*-value	*F*-ratio	*P*-value
Calcium-stimulated PLA_2	12.90	<0.0001	9.20[a]	<0.0001[a]
Calcium-independent PLA_2	5.21	<0.0001	1.76[b]	NS[b]
Lysophospholipase	8.95	<0.0001	1.15[a]	NS[a]
Acyltransferase	7.82	<0.0001	0.65[c]	NS[c]
GPCPD	77.02	<0.0001	2.90[a]	<0.01[a]
Choline kinase	2.37	<0.01	0.49[a]	NS[a]
Ethanolamine kinase	3.00	<0.01	0.68[a]	NS[a]
PCCT	3.47	<0.001	2.21[a]	<0.05[a]
PECT	7.10	<0.0001	7.30[a]	<0.0001[a]
Choline phosphotransferase	1.25	NS	0.65[a]	NS[a]

Values shown are the *F*-ratio and *P*-value of the one-way ANOVA of enzyme activities in all 12 brain regions, or in 11 regions excluding white matter, substantia nigra, or cerebellum as indicated. NS, not significant. Abbreviations for enzymes as defined in the text.

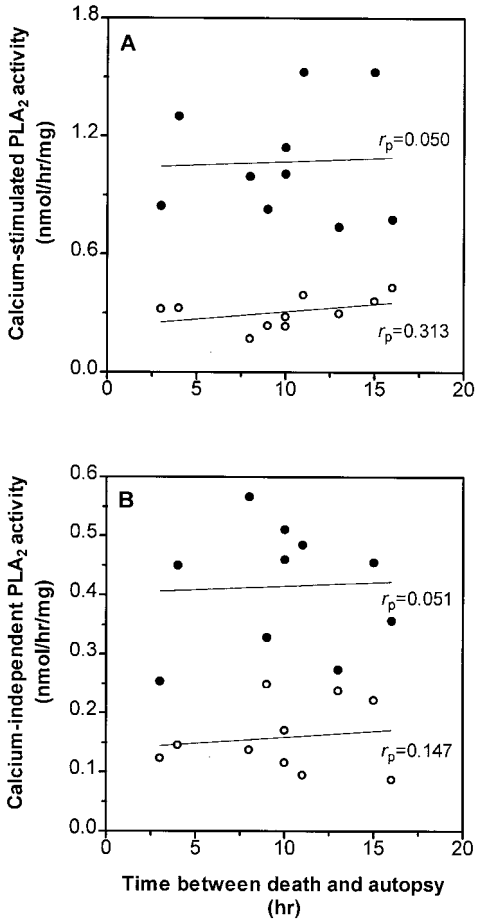

Fig. 2. Lack of correlation between (A) calcium-stimulated and (B) calcium-independent PLA_2 activity and the time interval between death and autopsy, in human temporal cortex (filled points) and substantia nigra (open points). The best-fit linear regression line through the points is shown for each set of values along with the Pearson correlation coefficient (r_p).

distribution, was strikingly high in the cerebellum. Recent evidence has suggested this enzyme constitutes the major route of fatty acid uptake into the cell, as opposed to *de novo* synthetic mechanisms.[2] Thus, our observation suggests that the cerebellum may have a greater requirement for fatty acid sequestration than other brain structures.

Enzymes possessing low activity in substantia nigra compared to other brain regions

The major aim of our study was to determine whether the activities of one or more phospholipid metabolizing enzymes were different in the substantia nigra compared to those in other regions of the human brain. Of all the enzymes investigated, calcium-stimulated PLA_2 possessed the most heterogeneous distribution within the brain, especially in comparision to calcium-independent PLA_2, as well as metabolically-related enzymes such as acyltransferase and lysophospholipase. This may be explained by the cellular use of some PLA_2 types, including the calcium-stimulated form(s), for functions other than phospholipid turnover e.g., signal transduction, which are likely more heterogeneously distributed within the brain. Thus, the higher calcium-stimulated PLA_2 activity of cortical areas may derive more from the participation of the enzyme in these other processes, rather than suggesting an increased rate of membrane breakdown. It is unlikely however that low nigral PLA_2 activity, can be explained similarly, since the activity of both PCCT and PECT (the rate limiting enzymes of PC and PE synthesis, respectively), which in general did not appear correlated with PLA_2 activity (compare Fig. 1A,B with Fig. 3C,D), were also low in this brain region. Importantly, low nigral PLA_2 activity was observed under a variety of conditions, i.e. (i) using both PC and PE as substrate, (ii) in the presence or absence of calcium, and (iii) in homogenates or particulate fraction salt extracts, suggesting that this phenomena might not be confined to a specific isoform of the enzyme. However, we cannot rule out that low activity of a single isoform, comprising the dominant

Table 3. Activity of phospholipase A_2 assayed at pH 8.5 in the presence of 1 mM calcium chloride in potassium chloride extracts of the particulate fraction[16] of indicated regions of four human brains using either 50 μM 1-palmitoyl, 2-[^{14}C]-arachidonyl phosphatidylethanolamine or 50 μM 1-stearoyl, 2-[^{14}C]-arachidonyl phosphatidylcholine

Brain region	Phosphatidylethanolamine (nmol/h/mg protein)	Phosphatidylcholine (nmol/h/mg protein)
Temporal cortex	8.2 ± 1.4	1.2 ± 0.2
Hippocampus	7.2 ± 1.1	1.0 ± 0.2
Cerebellum	6.4 ± 1.2	0.9 ± 0.2
Substantia nigra	3.4 ± 1.1	0.5 ± 0.1

Table 4. Lack of inhibition of cortical, hippocampal and cerebellar phospholipase A_2 activities by extracts of human substantia nigra

	Calcium-stimulated PLA_2 activity (pmol/h)			Calcium-independent PLA_2 activity (pmol/h)		
		Assayed with 10 μg substantia nigra protein			Assayed with 10 μg substantia nigra protein	
Brain region	Assayed individually	Expected	Actual	Assayed individually	Expected	Actual
Temporal cortex	14.8 ± 2.0	21.2 ± 2.5	19.5 ± 2.5	5.5 ± 1.1	7.6 ± 1.2	8.2 ± 1.8
Hippocampus	13.3 ± 2.4	19.7 ± 3.0	21.2 ± 5.1	4.7 ± 0.8	6.9 ± 0.9	5.6 ± 0.9
Cerebellum	9.6 ± 1.2	16.2 ± 1.8	14.3 ± 2.0	3.9 ± 0.6	6.1 ± 0.7	5.5 ± 1.0
Substantia nigra	6.4 ± 0.7	NA	NA	2.2 ± 0.3	NA	NA

Homogenates of the indicated brain regions (n = 5 subjects) containing 10 μg of protein (half the normal amount) were assayed for calcium-stimulated or calcium-independent PLA_2 activity (see Table 1) either alone, or in the presence of 10 μg of substantia nigra homogenate protein prepared from the same brain. The expected PLA_2 activity of each preparation assayed in the presence of nigral homogenate (the sum of activities of each preparation assayed alone), was not significantly different from the observed value when compared using paired, two-tailed Student's t-tests ($P > 0.2$ in all cases).

PLA_2 activity in human brain, is responsible for our observations.

The relatively low activity of PLA_2, PCCT and PECT in the substantia nigra compared to that in other brain regions is unlikely to be due to a more rapid rate of denaturation *post mortem* in the nigra since we did not observe any significant association between enzyme activity and the time interval between death and autopsy of each subject over a large range (3–17 h). Furthermore, given that we could not detect significant inhibition by nigral preparations of the PLA_2 activities of other brain regions (see Table 4), it appears likely that the substantia nigra contains less, or less active, PLA_2, rather than this brain region containing an endogenous PLA_2 inhibitor. In addition, since calcium-stimulated PLA_2 activity is also low in largely lipid-free salt extracts of the substantia nigra, it is unlikely that differences in membrane composition of nigral cells vs those in other brain regions could account for our observations. However, we cannot rule out the possibility that the differing white matter activity of several of the studied enzymes, especially the predominantly membrane-associated enzymes PLA_2, lysophospholipase, acyltransferase, and PCCT,[15,16,18] could be due to the significantly different membrane characteristics of white vs gray matter.[5]

PLA_2 plays an important role in the removal of free radical damaged phospholipid molecules, both by its preference for oxidized phospholipids[1,12,21,26] and by being required for the action of glutathione peroxidase.[9,25] Thus, low activity of PLA_2 in the substantia nigra may slow the detoxification of oxidized phospholipids, thereby leading to the accumulation of toxic lipid peroxides in the membrane. Indeed, inhibition of PLA_2 in rat liver leads to an accumulation of oxidized membrane phospholipids following induction of peroxidation by ferrous ions.[3] Lipid peroxides not removed in a timely manner may initiate a cascade of oxidation events, since these compounds can form lipid free radicals capable of oxidizing neighbouring phospholipids[8,11] and proteins,[8] as well as decaying into protein-reactive aldehydes.[8] Although a form of glutathione peroxidase has been identified which does not require prior removal of the oxidized fatty acid by PLA_2,[27] the products of this peroxidase reaction, hydroxy fatty acids, are more polar than their lipid peroxide precursors, and hence are disruptive to membrane structure and integrity.[28] Low PLA_2 activity would be expected to slow the removal of hydroxy fatty acids from the membrane, thereby increasing the likelihood that membrane integrity will be compromised.

In addition, the relatively low activity of PCCT and PECT in the substantia nigra suggests that the ability of nigral neurons to resynthesize quickly new phospholipid molecules is limited. Hence, low activity of PLA_2, PCCT, and PECT in the substantia nigra may render neurons within this brain region less capable of responding to oxidative insult, thereby

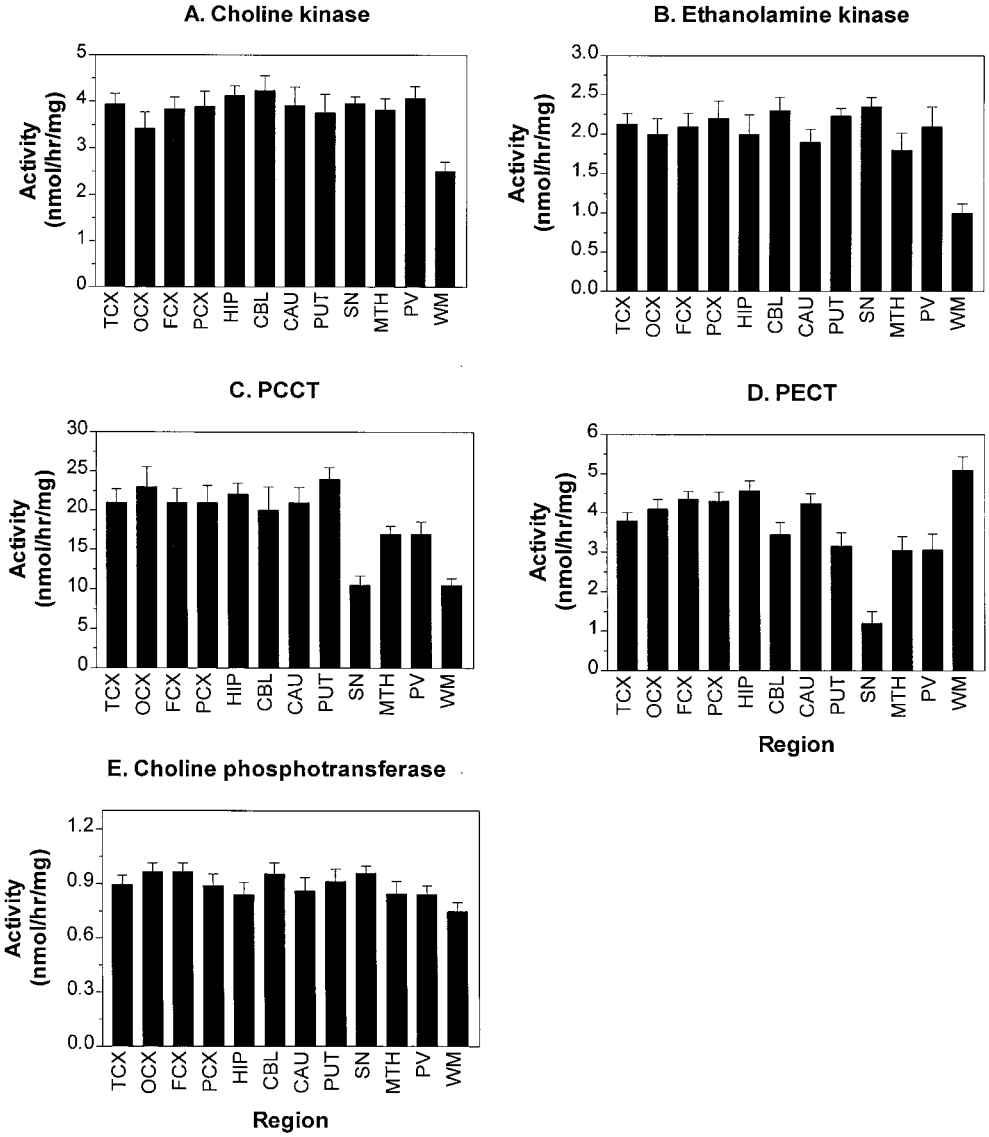

Fig. 3. Regional distribution of phospholipid synthetic enzymes in the autopsied human brain. Values shown are mean activity of 10 subjects except for medial thalamus and pulvinar when seven subjects were used. Bars indicate the S.E.M. TCX, temporal cortex; OCX, occipital cortex; FCX, frontal cortex; PCX, parietal cortex; HIP, hippocampus; CBL, cerebellar cortex; CAU, caudate; PUT, putamen; SN, substantia nigra; MTH, medial thalamus; PV, pulvinar; WM, subcortical white matter.

contributing to cell stress and death. Such a feature of nigral cells may leave them more vulnerable to damage by free radicals and contribute to the neurodegenerative process of PD.

CONCLUSIONS

In summary, we found that the activity of most enzymes of phospholipid metabolism possess a relatively uniform distribution in the human brain. However, the exceptions to this rule, namely PLA_2, PECT, and PCCT in the substantia nigra, suggest potentially important inter-regional differences in this metabolic system, which may have relevance to the integrity of these brain regions in both the normal and diseased state.

Acknowledgements—This work was supported by US NIH NINDS grant no.26034. BMR is an Ontario Mental Health Foundation scientist.

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(*Accepted* 4 *August* 1997)