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Do organic solvents induce changes in the dopaminergic system? Positron emission tomography studies of occupationally exposed subjects

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Abstract *Objectives*: The objective of this study was to test the hypothesis that long-term occupational exposure to organic solvents may effect the levels and turnover of dopamine in man. *Methods*: A study was performed on 17 patients with neuropsychiatric symptoms due to occupational solvent exposure, and 11 healthy non-exposed male volunteers (controls). Positron emission tomography (PET) was used to assess striatal dopaminergic function, using L-[^{11}C]DOPA, [^{11}C]nomifensine and [^{11}C]raclopride as tracers. *Results*: The rate of dopamine synthesis was significantly increased among subjects with occupational exposure to organic solvents compared with non-exposed controls. After controlling for the difference in age between exposed and controls, the effect of solvent exposure became less apparent and was reduced from +32% (P = 0.009) to +25% (P = 0.07). There were no differences with regard to the binding of [^{11}C]nomifensine. Patients with and without the diagnosis of toxic encephalopathy did not differ with regard to their putaminal uptake of L-[^{11}C]DOPA, [^{11}C]nomifensine and [^{11}C]raclopride. *Conclusion*: The data support the hypothesis that long-term exposure to organic solvents may increase the rate of dopamine synthesis in the brain without affecting the number of presynaptic terminals or postsynaptic dopamine receptors.

Key words Dopamine · Organic solvents · Positron emission tomography · Toxic encephalopathy

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Introduction

Several cross-sectional studies, based on psychological testing, have shown that long-term exposure to organic solvents may impair functions of the central nervous system, in particular, memory, concentration, and perceptual and psychomotor speed and accuracy (Baker 1994). A World Health Organization meeting in 1985 concluded that long-term occupational exposure to organic solvents may cause adverse effects on the central and peripheral nervous systems (WHO 1985). The same conclusion was reached at a workshop on neurobehavioural effects of solvents (Cranmer and Goldberg 1986) and by the National Institute for Occupational Safety and Health (NIOSH 1987). There are, however, some criticisms of the view that occupational inhalation of organic solvents may induce a chronic cerebral disease (Errebo-Knudsen and Olsen 1986; Grasso et al. 1984).

The clinical picture of long-term exposure to solvents is dominated by vague and non-specific symptoms and there are no specific tests. For a diagnosis of solvent induced toxic encephalopathy (type 2B; Cranmer and Goldberg 1986) according to the criteria set for insurance compensation in Sweden, the following requirements should be met: long or heavy exposure to organic solvents or both; relevant symptoms, such as increased fatigue, memory impairment, difficulties in concentration, and personality changes such as passivity; presence of pathological findings in terms of an objective measure (e.g. impaired performance in a psychometric test); a relation in time between exposure and the development of symptoms and signs; and no other obvious cause for the disease (Edling 1985).

One of the criticisms raised against the possibility of a toxic encephalopathy due to occupational exposure to organic solvents is that there are no animal studies indicating such effects. However, a few experimental studies suggest that exposure to toluene and other organic solvents can affect the levels and turnover of catecholamines including dopamine (Fuxe et al. 1982; Mutti et al. 1988; von Euler et al. 1987, 1989, 1990, 1991, 1993).

To test further the hypothesis that occupational exposure to organic solvents can affect the dopamine system, we have started studies on healthy volunteers and on patients referred to the Department of Occupational and Environmental Medicine because of neuropsychiatric symptoms due to solvent exposure. Positron emission tomography (PET) was used to assess striatal dopaminergic function using the following tracers: L-[^{11}C]DOPA for decarboxylase activity in the in vivo synthesis of dopamine, [^{11}C]nomifensine for number of presynaptic dopaminergic terminals and [^{11}C]raclopride for the quantification of D_2-dopamine receptors.

In this introductory study we present data on 17 patients with neuropsychiatric symptoms after long term occupational exposure to organic solvents. They were, after clinical evaluation, classified as type 1 (symptoms only) or type 2B (symptoms and impairment in intellectual function) according to the proposed categorization by Cranmer and Goldberg (1986).

The study was approved by the Ethics Committee of the Faculty of Medicine, University of Uppsala and the Isotope Committee at the University Hospital in Uppsala, and all subjects gave informed consent.

Material and methods

Subjects

Seventeen male patients, mean age 52 ± 7 years, with long-term occupational exposure to organic solvents, mean exposure time 23 ± 8 years, were studied and compared with 11 healthy male volunteers, with a mean age of 44 ± 7 years. The patients were recruited from among those who had been referred to the Department of Occupational and Environmental Medicine at the University Hospital, Uppsala between 1983 and 1992 because of a suspicion that their symptoms were caused by occupational exposure to organic solvents. They had had at least 10 years of exposure and the core symptoms were increased fatigue, memory impairment, difficulties in concentration and personality changes. When examined at our department the patients answered a screening questionnaire for neuropsychiatric symptoms, the so-called Q 16 (Axelson and Hogstedt 1988), and underwent psychometric testing, with a standardized test battery for investigating functional disorders (Ekberg et al. 1988). All 25 patients who, on the basis of the clinical examination, were believed by the physician to have solvent-related symptoms, were asked to participate in the study and 17 agreed to do so. Of the 17, nine had symptoms only (type 1) and eight were diagnosed as having a mild toxic encephalopathy based on symptoms and impairments in the psychometric test profile (type 2B).

Before the PET study, the patients were examined once again and asked to answer the Q 16. Their occupational history and symptomatology was checked by a specialist in occupational medicine and they underwent a medical examination by a neurologist to exclude other possible causes of their symptoms. None of the patients showed any signs of hypokinetic or hyperkinetic extrapyrimidal symptoms. No new psychometric tests were performed. Nine of the patients had worked as house painters, six as spray painters, one in a printing office and one had been exposed to styrene in boat building. There were no hygienic measurements of exposure levels, and therefore "years of exposure" was used as a measurement for exposure. The patients had mostly been occupationally exposed to different mixtures of solvents, which made it impossible to subdivide the patient group into different exposure groups with regard to type of solvent. At the time of the examination, all but four had been unexposed for several years. Amongst those with a diagnosis of mild toxic encephalopathy, only one was still exposed compared with three of those without the diagnosis.

The 11 referents were recruited on a voluntary basis. They had no occupational exposure to organic solvents and no known cerebral disorder or psychiatric disease. We aimed to recruit referents of the same sex and about the same age as the patients. However, the final group of healthy volunteers was slightly younger (mean age 44 ± 7 years) than the patients. All referents underwent a medical examination before the study.

Radiochemistry

The radionuclide ^{11}C was produced by the $^{14}N(p,\alpha)^{11}C$ nuclear reaction using 17 MeV protons in an M17 cyclotron (Scanditronix AB, Uppsala, Sweden) and obtained as [^{11}C]carbon dioxide. [^{11}C]Raclopride and [^{11}C]nomifensine were produced from the corresponding demethylated analogues by *N*-alkylation with [^{11}C]methyl iodide (Långström et al. 1987). The synthesis of L-[^{11}C]DOPA, radiolabelled in the β-position, was carried out using a combination of organic synthetic and multienzymatic procedures (Bjurling et al. 1990). After analysis for identity and chemical and radiochemical purity, the samples were passed through a 0.22-μm filter before being administered intravenously to the subjects. The radioactive dose of each tracer varied from 180 to 770 MBq corresponding to a total injected amount of 10–25 μg.

Positron emission tomography (PET)

PET was performed with the subject lying with the head fixed in the eight-ring positron emission tomographic camera (GE2048-15B or GE 4096-15WB Plus, from General Electric Medical Systems, Uppsala, Sweden). The two scanners enable simultaneous measurement of the distribution of radioactivity from the 15 transaxial slices 6.5 mm apart and with an in plane resolution of 6 mm (Holte et al. 1989, Kops et al. 1990) full width half maximum.

Fixation and positioning

Subjects were positioned in the scanner so that the most basal slice corresponded to the orbito-meatal line. Fixation was achieved through foam-padding supported by a Plexiglas headrest and a broad adhesive tape across the forehead which was attached to the headrest. The tomograph was started with the injection of the tracer. The radioactivity in each sequential time frame was collected for six 1-min frames, three 2-min frames and ten 200-s frames for L-DOPA, and for nomifensine and raclopride during ten 1-min frames, ten 2-min frames and six 200-s frames, respectively. Images were reconstructed for each sequential time-frame with a 4.2-mm Hanning filter, 2 mm pixel size and using contour finding for attenuation correction (Bergström et al. 1982). For the delineation of regions of interest, summation images were reconstructed using images obtained 20–45 min after radiotracer injection of L-DOPA and 20–50 min after injection of raclopride and nomifensine, respectively (Fig. 1).

Calculations of PET data

For the calculation, regions of the brain were delineated with standardized size and shape and identified on summation images. This was done without knowledge of the history of the study subjects. The following regions were delineated: the putamen on the right and left side in at least two slices. A reference area was obtained in the L-DOPA studies by delineating a whole brain region two slices below the slice with the highest putaminal radioactivity (Hartvig et al. 1991). For the nomifensine and raclopride studies a reference region including the cerebellum was chosen in one slice where cerebellum was clearly delineated from the temporal cortex.

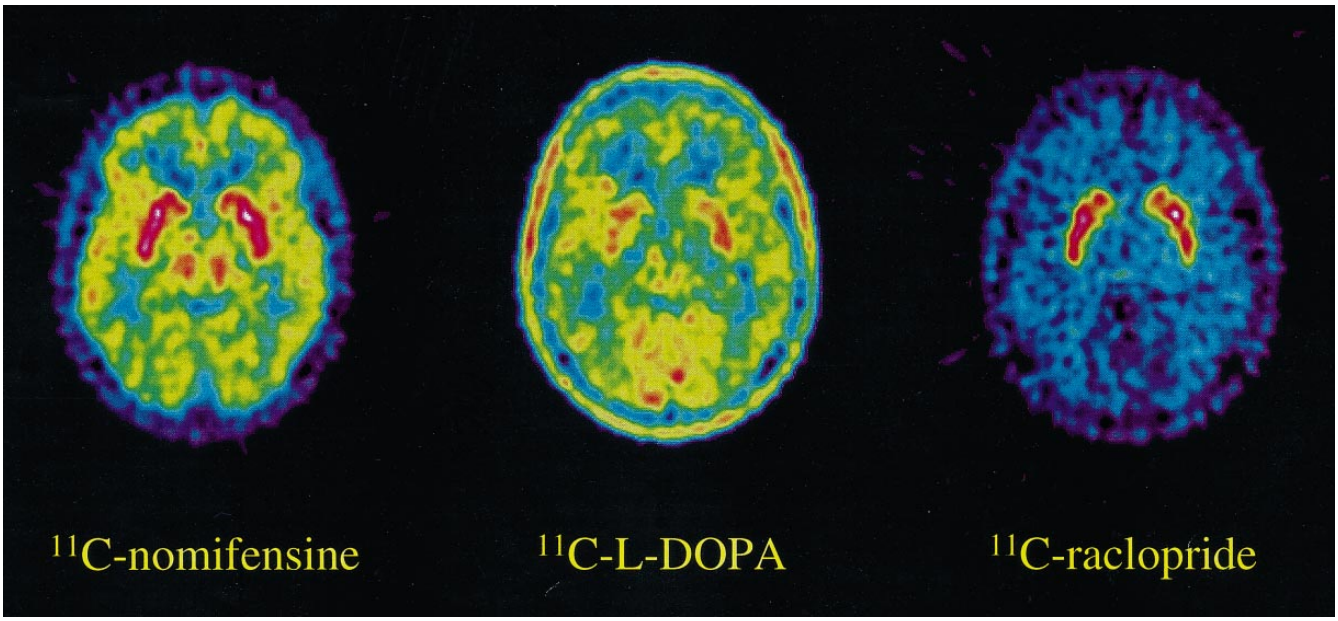

Fig. 1 Positron emission tomography (PET) images showing the three different ^{11}C-labelled tracers used to assess striatal dopaminergic function in solvent-exposed subjects

L-DOPA

The radioactivity in putamen in relation to that of the reference region was described using a reduced compartment model comprising one compartment for radioactivity in the extracellular space and one compartment for specific utilization of radioactive tracer (Hartvig et al. 1991; Tedroff et al. 1992). The analysis yields a rate constant, k_3, for striatal utilization of ^{11}C-L-DOPA radioactivity that is assumed to represent the rate constant for transport and conversion of the tracer to [^{11}C]dopamine within the region of interest.

Nomifensine and raclopride

The regional receptor binding of nomifensine and raclopride was calculated using a two-compartment model (Salmon et al. 1990; Tedroff et al. 1990). The reference region was assumed to be similar to the target region in terms of transport of tracer into the brain and to have an insignificant density of specific dopamine terminals or dopamine receptors. Following equilibration reached after 20 min, the relation between radioactivity in the putamen and the reference region minus unity (C_{put}/C_{ref} –1) was assumed to equal B_{max}/K_d, where B_{max} is the concentration of non-occupied receptors and K_d is the equilibrium dissociation constant (Farde et al. 1989).

Statistical analysis

The Mann-Whitney *U*-test was used in all comparisons of individual parameters between the different groups. The least squares linear regression analysis was used to analyse the correlation between the rate of dopamine synthesis in the putamen and (i) the uptake of nomifensine in the same region of the brain, (ii) the results from the screening questionnaire for neuropsychiatric symptoms, and (iii) the number of years of occupational exposure to organic solvents. To control for the different age structure among the referents and the occupationally exposed individuals, analysis of covariance was made using a one-way ANCOVA test with age as the covariate, exposure as the independent factor and the rate of dopamine synthesis in the putamen as the dependent variable. Two-tailed statistics were used in all calculations and the level of significance was set at 5%.

Results

As shown in Table 1, the group of patients with long-term occupational exposure to organic solvents had a higher rate of dopamine synthesis in the putamen than the referents (P = 0.009). There was no difference between these two groups with regard to their binding of [^{11}C]nomifensine (Table 2). According to the linear regression analysis, there was a weak correlation (r = 0.38, P = 0.08) between the rate of dopamine synthesis and uptake of nomifensine in the putamen, when all individuals receiving both L-[^{11}C]DOPA and [^{11}C]nomifensine (n = 22) were pooled into one group. For the exposed this correlation was r = 0.47 (P = 0.07) and for the controls r = 0.52 (P = 0.29), respectively.

The referents were, on average, 8 years younger than the solvent-exposed patients (Table 1). After using ANCOVA to control for the age difference, the effect of exposure on the increased rate of dopamine synthesis be-

Table 1 Rate of dopamine synthesis in putamen of subjects with and without occupational exposure to organic solvents. Mean value, standard deviation (SD) and range (min–max) for age and putaminal rate of dopamine synthesis ([^{11}C]-L-DOPA) among male patients with a history of occupational exposure to organic solvents (n = 17) compared with unexposed male referents (n = 11). The dopamine turnover is expressed as the decarboxylation rate of dopamine per minute ($k_3 \times 10^{-2}$ min^{-1}). Statistical significance was judged using the two-tailed Mann-Whitney two-sample test

Group	Age (years)		[^{11}C]L-DOPA ($k_3 \times 10^{-2}$ min^{-1})	
	Mean ± SD	(Min–max)	Mean ± SD	(Min–max)
Referents	44 ± 7	(31–54)	1.27 ± 0.23	(0.94–1.60)
Patients	52 ± 7**	(37–63)	1.68 ± 0.46**	(0.56–2.23)

** $P < 0.01$

Table 2 Uptake of nomifensine in putamen of subjects with and without occupational exposure to organic solvents. Mean value, SD and range (min–max) for age and putaminal uptake of radioactivity from [^{11}C]nomifensine among male patients with a history of occupational exposure to organic solvents (n = 16[a]) compared with unexposed male referents (n = 6[b]). Statistical significance was judged using the two-tailed Mann-Whitney two-sample test

Group	Age (years)		[^{11}C]nomifensine	
	Mean ± SD	(Min–max)	Mean ± SD	(Min–max)
Referents	43 ± 9	(31–54)	1.84 ± 0.12	(1.70–2.04)
Patients	52 ± 7*	(37–63)	1.84 ± 0.15	(1.58–2.12)

* $P < 0.05$
[a] The [^{11}C]nomifensine data from one patient are missing due to technical error
[b] Only 6 of the 11 referents given [^{11}C]-L-DOPA were offered a second injection with [^{11}C]nomifensine

came less apparent ($F_{1,25}$ = 3.48, P = 0.074, compared with P = 0.009 for the Mann-Whitney test), the adjusted means for the rates being 1.32×10^{-2} (SD: ± 0.129) × min^{-1} and 1.65×10^{-2} (SD: ± 0.101) × min^{-1} for the referents and the exposed group, respectively. Consequently, after controlling for the difference in age, the effect of exposure on the rate of dopamine synthesis was reduced from +32% to +25%.

When the solvent-exposed patients were divided into two groups depending on whether or not they had received a diagnosis of toxic encephalopathy, those with the diagnosis (type 2B) were found to have more (P = 0.009) yes-answers in the Q16 questionnaire than those without (type 1) (Table 3). However, there were no significant differences in the rates of dopamine synthesis, binding of nomifensine and raclopride, or age between the two groups of patients.

There was no significant correlation between the rate of dopamine synthesis and the number of yes-answers in the Q 16 questionnaire or between the rate of synthesis and the number of years of occupational exposure to organic solvents.

Discussion

Recent information from experimental studies in animals (von Euler et al. 1987, 1989, 1990, 1991, 1993) has indicated that solvent exposure may interfere with basic dopamine function and formed the basis of the present study protocol using several tracers for the study of different aspects of dopaminergic function in humans. Our results indicate that the rate of dopamine synthesis was increased in subjects with occupational exposure to organic solvents compared with non-exposed controls. After controlling for the difference in age, the effect of exposure on the rate of dopamine synthesis was reduced from +32% to +25%. There was no difference with regard to the binding of [^{11}C]nomifensine. The data support a hypothesis that long-term organic solvent exposure may increase the rate of dopamine synthesis in the brain without affecting the number of presynaptic terminals or postsynaptic dopamine receptors.

The use of ^{11}C-L-DOPA has been extensively validated in previous studies (Tedroff et al. 1991, 1992, Lindner et al. 1995). The magnitude of k_3 appears to be dependent on the activity of the aromatic amino acid decarboxylase enzyme (EC 4.1.1.28) reflecting the dopamine synthesis rate. (Tedroff et al. 1991, 1992; Lindner et al. 1995). Moreover, when performing experiments with ^{11}C-L-DOPA labelled in another (the carboxylic) position, radioactivity it is not specifically trapped in striatal areas as the radiolabel is lost by decarboxylation in the form of rapidly equilibrating carbon dioxide (Tedroff et al. 1992). Furthermore, the calculated dopamine synthesis rate was found to be similar following measurement with PET as compared with bioanalysis of ^{11}C-L-DOPA, formed ^{11}C-dopamine and metabolites in the brain homogenate from animals (Lindner et al. 1995).

By using L-DOPA in studies of the dopaminergic function, the derived rate of dopamine synthesis includes the decarboxylation process of ^{11}C-L-DOPA to dopamine. For the true rate of dopamine synthesis to be obtained, the size of the precursor pool also needs attention. In addition, if

Table 3 Rate of dopamine synthesis and uptake of nomifensine and raclopride in putamen of solvent-exposed subjects with and without a diagnosis of toxic encephalopathy (Type 2B). Mean value and SD for age, number of yes-answers in a questionnaire for neuropsychiatric symptoms (Q 16), rate of putaminal dopamine synthesis ([^{11}C]-L-DOPA; $k_3 \times 10^{-2}$ min^{-1}), and binding potential of nomifensine ([^{11}C]NOM, 20–40 min) and raclopride ([^{11}C]RAC, 20–50 min) in putamen among patients with occupational exposure to organic solvents, but without diagnosis of toxic encephalopathy (n = 9), compared with patients with occupational exposure to organic solvents with this diagnosis (n = 8). Statistical significance was judged using the two-tailed Mann-Whitney two-sample test

Patients	Age (years) (mean ± SD)	Q 16 (mean ± SD)	[^{11}C]DOPA (mean ± SD)	[^{11}C]NOM (mean ± SD)	[^{11}C]RAC (mean ± SD)
Without diagnosis (type 1)	53 ± 6	7.2 ± 3.4	1.86 ± 0.31	1.84 ± 0.18	4.27 ± 0.33
With diagnosis (type 2B)	52 ± 8	12.4 ± 2.9**	1.47 ± 0.52	1.83 ± 0.11[a]	4.28 ± 0.53[b]

** $P < 0.01$
[a] n = 7, the [^{11}C]nomifensine data from one patient are missing due to technical error
[b] n = 7, one of the patients given [^{11}C]-L-DOPA and [^{11}C]NOM refused a subsequent injection with [^{11}C]RAC

the resulting dopamine level in the brain is the issue, the clearance processes of dopamine also need to be considered. Thus, the rate serves to characterize the activity of enzymes involved rather than the actual amount of dopamine produced or the dopamine levels obtained. Higher values for the rate imply an enhancement of the catalytic activity of dopadecarboxylase (Hartvig et al. 1991; Tedroff et al. 1992). In this context it is of interest that certain organic solvents, including toluene, have been reported to stimulate the catalytic activity of dopadecarboxylase in experimental animals (Bowsher and Henry 1986).

There was no significant difference between those patients with a diagnosis of toxic encephalopathy (type 2B) and those without (type 1). Those with a diagnosis had clearly more positive answers on the Q 16 but a lower rate of dopamine synthesis in the putamen. The reason for this is not known. It may be a chance finding, due to, for example, small numbers in the studied groups, or indicate that the subtle changes have no correlation with the impaired performance in psychometric tests. Neither was there any significant correlation between years of exposure and dopamine synthesis rate. Perhaps this should not be expected since it has been shown that although classification of exposure by duration alone is a reasonable predictor of classification by cumulative dose estimate, it might result in misclassification of about one-third of the subjects and it is a poor surrogate for intensity of exposure (Glass et al. 1994).

It would have been beneficial if we could have classified the patients into specific exposure groups, i.e. exposed to toluene, styrene, etc. However, as pointed out earlier, most of the patients were exposed to mixtures of solvents, which made such a subclassification impossible. Furthermore, the group was too small to make a classification into different job categories meaningful. Since the rationale behind the study was animal data on toluene exposure one could dispute whether other solvents should have the same effects. Many organic solvents have the capacity to produce neurotoxicity (NRC 1992), but despite extensive research, the mechanism for these effects are still unknown. One mechanism proposed is that solvents interfere with the synthesis of neurotransmitters (NRC 1992). This was also the hypothesis tested in the present study and there are no scientific data contradicting our belief that this could be a mechanism common to most organic solvents, not only toluene. However, the ideal situation would be to study a group with exposure to one single solvent. This should preferably be done in an experimental situation.

The present study may have some limitations due to a selection process operating before the patients' first contact with the clinic. However, neither at the first nor at the second examination were there any indications that the patients suffered from other diseases or from severe neurological or psychiatric disorders. It is also difficult to see a selection mechanism whereby subjects with an alteration in dopamine function would be more apt to participate in the study. In fact it might be postulated that it is more reasonable to believe that patients without other serious diseases are more prone to participate in a follow-up study. Therefore, we do not believe that a particular strong selection mechanism biased the results.

The dopamine re-uptake inhibitor nomifensine radiolabelled with ^{11}C quantitates the number of dopaminergic terminals (Tedroff et al. 1990). Nomifensine is a high-affinity ligand for specific binding to presynaptic monoaminergic reuptake sites in the brain. The information gained by [^{11}C] nomifensine relates to the number of binding sites and their affinity (Tedroff et al. 1990) and is commonly interpreted in structural terms, i.e. as monoaminergic synapse density. Thus, our data give no indications of structural changes in the dopaminergic system in putamen, associated with long term exposure to organic solvents.

The single study with high, specific radioactivity of [^{11}C]raclopride allowed the density (B_{max}) of unbound dopamine D_2 receptors to be measured relative to the affinity constant (K_d) of raclopride receptor binding. This binding did not differ between those subjects with and without a diagnosis of toxic encephalopathy, indicating that the receptor qualities were similar in the two groups. However, changes in B_{max} and/or K_d cannot be excluded on the basis of the results of this study, since any change in receptor density would be accompanied by a matching reverse change in affinity.

The battery of tracers for the assessment of brain dopaminergic function used in the present study has previously been utilized in experimental studies of the toxic effects of 1,2,3,6-tetrahydro-1-methyl-4-phenylpyridine (MPTP) (Leenders et al. 1988) and in studies following chronic manganese exposure in the monkey (Eriksson et al. 1992). A loss of dopaminergic terminals in the corpus striatum was accompanied by a lower rate for dopamine synthesis following acute MTPT administration (Leenders et al. 1988). On the other hand, although the number of dopaminergic terminals in the monkey decreased with repeated manganese exposure, the rate of dopamine synthesis was unchanged (Eriksson et al. 1992). This parallels the effects of copper accumulation on the brain dopaminergic system in Wilson's disease, where a loss of postsynaptic dopaminergic receptors was obvious (Westermark et al. 1995). In the present study we found that with an increasing number of presynaptic terminals the dopamine synthesis increased. This correlation was almost significant among the solvent-exposed patients, indicating a different toxic action to the dopaminergic system of solvents as compared with metals.

We have found only one study in which an individual with occupational exposure to an organic solvent was evaluated with PET. This individual was accidentally exposed to tetrabromoethane, and was investigated with a PET scan with ^{18}F-2-deoxyglucose to assess regional cerebral metabolic activity. Decreased glucose metabolism was found in the left temporo-parietal cortical region and right subcortical (basal ganglia, amygdala, hippocampus) structures. Neuropsychological tests revealed impairment in learning and memory, attention and psychomotor speed. The turnover of dopamine was not investigated (Morrow et al. 1990).

The effects of subacute exposure to organic solvents, in particular toluene, on the dopaminergic system have been extensively investigated in rodents (Mutti et al. 1988; von Euler et al. 1991, 1993). These studies have shown that exposure to toluene may affect both tissue levels and the turnover of catecholamines, including dopamine. Effects on dopamine levels and turnover seem to vary, depending not only on the duration of exposure and the inhaled concentration of toluene, but also on the region of the brain investigated. In the rat, subacute exposure to toluene (500–1000 ppm) caused an increase of noradrenaline and dopamine stores within the median eminence, and an increase of noradrenaline turnover in the median eminence and certain hypothalamic nuclei (Andersson et al. 1980, 1983). On the other hand, decreased dopamine levels and turnover were seen in certain areas of the anterior caudate nucleus and the nucleus accumbens of rats following subacute toluene in exposure doses of 80–500 ppm (Fuxe et al. 1982). We have found no studies of the effect of long term toluene exposure on dopamine synthesis in animals.

The changes in turnover of dopamine may be related to changes in monoamine receptor binding. Toluene exposure appears preferentially to affect dopamine D_2-receptors, causing reduced receptor affinity (von Euler et al. 1987, 1991). The effect on the D_2-receptor is believed to be due to a change in membrane fluidity (von Euler et al. 1987). The fact that toluene exposure in vitro may increase membrane fluidity (Edelfors and Ravn-Jonsen 1989) and reduce D_2 receptor affinity (von Euler et al. 1989) supports this mechanism. Such a mechanism may also be in line with the increased catalytic activity of dopadecarboxylase, found in patients. Thus, a complex interaction on dopamine synthesis and receptor binding is obvious after exposure to organic solvents and hence requires a battery of techniques for its full understanding. The midbrain dopaminergic projections are the nerve tracts within the brain that has been by far the most extensively studied with PET. This is due to the fact that the accumulation of dopaminergic pathways in the substantia nigra-corpus striatum area gives a high radioactivity contrast compared with the surrounding brain. Therefore, the present paper focused on the dopaminergic system in putamen, but solvent-induced effects on the central nervous system are most likely also to involve other neurotransmitters and regions of the brain.

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