International Journal of Occupational Medicine and Environmental Health, 2005;18(2):103 — 113

ORGANIC SOLVENTS AND THE DOPAMINERGIC SYSTEM

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Abstract
Organic solvents pose a considerable health risk for humans. It is due to their ability to cross biological barriers and indisputable toxicity on the one hand, and the wealth of applications and large production and consumption volumes on the other. The primary target of the toxic action of organic solvents is the nervous system. In this paper, some literature data showing that dopaminergic neurons and their projections are particularly susceptible to the toxic solvent action are presented.

Key words:
Organic solvents, Dopaminergic system, Parkinsonism, Parkinson's disease, Drug abuse, Pituitary function, Olfaction, Visual functions

INTRODUCTION

In spite of preventive measures imposed to limit the level of chemical contamination, the exposure-related health risk will long remain the subject of major concern to the mankind. One reason is the persistence of some contaminants in the environment (e.g., polychlorinated hydrocarbons, heavy metals). The second, and more important one, is the strong dependence of the attained civilization level on a widespread use of some chemical products. This situation makes knowledge of the exposure-related health risk a very important issue. There is no doubt that organic solvents are among the substances inseparably linked with our civilization.

The term organic solvents refers to a variable group of lipophilic and volatile substances. It includes aromatic and aliphatic hydrocarbons, alcohols, aldehydes, ethers and ketones. Listing all the possible applications of organic solvents is not necessary here. The fact that they are used as car fuels and lacquer and paint thinners is sufficient to realize the magnitude of the production and consumption volumes and the size of populations occupationally and nonoccupationally exposed to these substances. (It is quite likely that in the whole living human population, persons exposed to solvents may outnumber those who have never been exposed). At the same time, there is no question that practically all solvents are toxic and that the nervous system is the most vulnerable target of their toxic action.

For a majority of commonly used solvents, the acute effects of exposure, most frequently by inhalation, are similar. This would imply a similarity of the toxic action mechanism. According to the classical view, the solvent action on the nervous system is nonspecific and related to the solvents' affinity to lipid constituents of brain cells. Thus, the high vulnerability of the nervous system to solvents would be a consequence of the high lipid content in the neural tissue [1]. However, the mechanism of solvent action may

* Received: February 7, 2005. Accepted: April 29, 2005.
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appear to be more specific. Some reports indicate the solvent interaction with integral enzymatic proteins of cellular membranes, including ATP-ases and cholinesterases [2,3] as well as with neurotransmitter receptors [1,4–6]. Moreover, some neurotransmitter systems appear to be exceptionally prone to alterations following solvent exposure. Some authors point to the dopaminergic system (DA system) as a particularly vulnerable neural target for the action of organic solvents [7]. In fact, numerous reported observations may be considered as either direct or indirect evidence for this supposition.

It is known that functional disturbances and structural changes within the DA system underlie variable disease states and clinical syndromes. It is likely then, that exposure to solvents may be one of the factors inducing these states or increasing the propensity for their development. The DA system is composed of several parts subservient to different functions. In this paper we will present some evidence that these functions may be altered by solvent exposure, and that changes in the DA system may be the causative factor.

THE DOPAMINERGIC SYSTEM

Properties of DA neurons

The high vulnerability of the DA system to solvent action results from the functional and morphologic properties of the dopaminergic neurons (DA neurons), which render them particularly susceptible to variable toxic insults.

The neurons synthesizing dopamine (DA) belong to the class defined by Woolf [8] as "global neurons"(this class includes also cholinergic, serotonergic and noradrenergic neurons). Neurons of this class are characterized by a large projection area, spontaneous pacemaker-like activity and persistent responsiveness to growth factors. The latter property enables long-term adaptive changes under the influence of exogenous factors, but also – paradoxically – it promotes neurodegeneration in advanced age [9]. This issue is extremely important if one considers the fact that DA neurons constitute only a tiny fraction (less than 0.005%) of the total number of brain neurons. In a 33 year-old man, the A 9 area, i.e. the area where more than 70% of the brain DA is synthesized, contains only about 450 000 DA neurons [10,11].

The axons of DA neurons are slow-conducting (about 0.5 m/s) small-diameter fibres and their conduction safety factor is low. At least in some brain areas (hypothalamus, ventral tegmental area (VTA), DA neurons are in a direct contact with the walls of capillary vessels [12]. This means a greater risk of exposure to exogenous substances present in blood. The DA effects on postsynaptic neurons are mainly inhibitory and the existing evidence indicates that DA is rather a neuromodulator than a neurotransmitter [13].

Anatomy of the dopaminergic system

In the mammalian central nervous system, DA synthesizing neurons are grouped in several locations [14] (Fig. 1). The largest group (A 9) is located in the substantia nigra pars compacta. The neurons of this group project mainly, although not exclusively, to striatum (nucleus caudatus and putamen), thus forming so called nigrostriatal DA projection system. The second by size group (A 10) is located in the ventral tegmentum (ventral tegmental area) in the vicinity of the nucleus interpeduncularis. Neurons of the A 10 group project to limbic forebrain structures (nucleus accumbens septi, septum, olfactory tubercle and amygdala) and to cortical areas (medial prefrontal cortex, entorhinal cortex, and possibly to the remaining neocortical and paleocortical areas). It is the mesocorticolimbic DA projection system. The third group (A 8) is located in the retrorubral area. The A 8 DA neurons share the projection areas with the A 9 and A 10 neurons and also form a bridge linking the A 9 and A 10 groups [15].

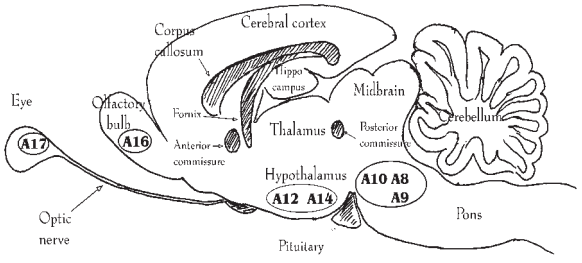

Fig. 1. Schematic view of the rat brain showing approximate position of DA neuronal groupings mentioned in the text.

Apart from the mesencephalic groups, there are several smaller groupings of DA neurons. In the hypothalamus, DA neurons (A 12 and A 14 groups) are located in the arcuate nucleus and in the periventricular nucleus. A part of these neurons project to the tuberal area, and some innervate directly the pituitary gland, medial and posterior parts. This is the tubero-infundibular DA projection (TIDA) system. DA is also synthesized by periglomerular cells in the olfactory bulb (A 16 group) and by innerplexiform cells of the retina (A 17 group).

THE DOPAMINERGIC SYSTEM: EFFECTS OF SOLVENT EXPOSURE

The mesencephalic DA neurons

Group A 9. The nigro-striatal dopaminergic projection system

The role of the dopaminergic nigrostriatal projection is to inhibit (presynaptically and postsynaptically) glutamate release from axonal endings activating the inhibitory GABAergic striatal neurons [16]. A decrease in the functional tone within this projection system results in an excessive inhibition of the striatum and characteristic behavioral manifestations known as parkinsonian symptoms (resting tremor, rigidity, bradykinesia, and postural reflex impairments). Parkinsonian symptoms may be induced by variable factors, including exposure to some toxic chemicals. A transient state characterized by the presence of these symptoms is referred to as parkinsonism. The parkinsonian symptoms are also characteristic of Parkinson's disease (PD), in this case, however, they intensify with time [17]. Idiopathic PD is a degenerative disease of the central nervous system. Its essence is a progressive decline of DA neurons mainly, but not exclusively, of the A 9 group [18]. PD becomes symptomatic when more than 90% of nigral DA neurons are lost.

In humans over 20 years of age, the physiological loss of mesencephalic DA neurons with age is estimated at 4–6% per decade [19]. Thus, what differs PD patients (about 1% of the population aged over 65 years) from healthy people of the same age is the magnitude of this loss [20,21]. Genetic endowment or environmental impact or a combination of both, is considered a possible cause of premature death of DA neurons in PD [22,23]. The results of comparative studies on homozygotic and heterozygotic twins have shown that the genetic factors are of etiological significance only in the early-onset PD (under 50 years of age), i.e. in about 10% of all PD cases. This finding indicates that the likely causes of the remaining 90% of cases are the environmental factors such as infections, traumas, and exposure to neurotoxins [24].

There is ample evidence showing that solvent exposure may affect the functional state of the nigrostriatal DA projection system. In a review paper published more than ten years ago, Tanner [17] mentioned three solvents among the substances able to induce the parkinsonian symptoms: carbon disulfide, n-hexane and methyl alcohol. Since that time, the reports of parkinsonism following solvent exposure have markedly increased in number and the list of parkinsonism-inducing solvents has been enriched with toluene [25], methanol [26,27], solvent mixtures [28,29], and trichloroethylene [30]. It is worth noting that in the cases reported by Kuriwaka et al. [29], treatment with DOPA resulted in disappearance of the symptoms proving their direct relationship with a deficit in the DA system. In the cases reported by Hageman et al. [28], however, the DOPA treatment was ineffective, indicating a postsynaptic deficit. In a study on mice, prompted by a case of parkinsonism after 7 years of occupational exposure to trichloroethylene, the authors have found that exposure to this solvent results in death of DA neurons in the substantia nigra [30]. Some experimental evidence of a damaging effect on the nigrostriatal system was also obtained for toluene [31]. It is assumed that exposure to neurotoxins, even at subsymptomatic doses, may reduce the viability of neurons and predispose them to premature death [32,33]. As a result, the age-related decline is hastened, which in case of the nigrostriatal DA neurons may mean that the threshold for appearance of the parkinsonian symptoms is attained earlier. One may then expect that PD cases will be more frequent in populations with a history of solvent exposure. The results of two studies confirm this supposition. In the first one, (a case-control questionnaire study, 86 PD patients and 86 controls), among the industrial chemicals to

which the subjects were occupationally exposed in the past only organic solvents were identified as significant risk factors for PD (OR – 2.78, 95% CI: 1.23–6.26) [34]. In the second study, PD patients with and without a history of solvent exposure were compared. The results revealed that exposure to hydrocarbon solvents directly correlated with disease severity and inversely with the latency period. The authors conclude that "...Occupations involving the use of hydrocarbon solvents are a risk factor for earlier onset of symptoms of PD and more severe disease throughout its course. Hence, hydrocarbon solvents may be involved in the etiopathogenesis of PD which does not have a major genetic component" [35].

Tu sum up, it appears that occupational exposure to at least some of the solvents results in an increased risk of PD at older age. Interestingly, no positive correlation was found between PD incidence and ethanol abuse. To the contrary, among the PD patients, the proportion of persons avoiding drinking (and smoking) was higher than in the control group [36, 37].

A 10 group: the VTA DA projection system

The broad projection areas of the A 10 group implies its contribution to the functions of multiple brain systems [38]. A simple and succinct formulation of the role of the VTA DA projection system has not yet been proposed. Possibly, the best one might be a responsibility for the initiation and coordination of behaviors aimed at satisfying needs. The key structure involved in this task is the nucleus accumbens (n.acc). The anatomical connections and functional properties of n.acc qualify it to the function "... as an interface between motivation and action" [39]. Lesion studies indicate that VTA and its projection areas are certainly involved not only in the initiation of behaviors but also in the assessment of the rewarding (or reinforcing) properties of the stimuli [40,41]. They are also the main place of the neuroadaptive changes induced by various drugs of abuse [42,43] and which manifest themselves as a persistent increase in behavioral and/or hormonal responses to the initiating drug (sensitization) and to other drugs (cross-sensitization). Some authors postulate that the development of these neuroadaptations relates directly to drug craving and drug dependence [42]. This statement is based on experimental findings showing that animals sensitized to a drug, e.g., amphetamine, prefer to stay in places when the drug is administered (place preference) and learn to self-administer the drug faster than nonsensitized controls do. One may then assume that the susceptibility to develop drug dependence and become a drug addict is largerly determined by the functional state of the mesocorticolimbic DA projection system and, consequently, by factors able to alter the functional state of this system. Similar suppositions were put forward by other authors as well [44,45].

Two following questions may arise in connection with the topic of the present paper:

1. Is the VTA DA projection system susceptible to the action of solvents?
2. Can exposure to solvents result in long-term changes in the VTA system, analogous to changes induced by drugs of abuse, and thus increase the propensity for drug dependence and addiction?

As to the first question, there is now no doubt that the activity of VTA neurons and their projection areas may change in response to solvent administration. The majority of data concerning this issue comes from studies on two substances, ethanol and toluene. It has been shown that ethanol, like cocaine and amphetamine, stimulates DA release in VTA and associated central striatum [46,47]. It is assumed that a common mechanism may be involved in the DA release by ethanol, amphetamine and cocaine although the pharmacological mechanisms for each of these drugs are entirely different [47]. Mecamylamine (a nicotinic antagonist) administered directly to VTA prevents the stimulation of DA release by ethanol, which indicates that this effect is mediated by nicotinic receptors in VTA [48].

In vitro studies on isolated VTA DA neurons and midbrain slices have shown that ethanol increases spontaneous activity of DA neurons and reduces afterhypolarization that follows spontaneous action potentials in these neurons. These observations have been regarded as evidence for a direct action of ethanol on DA neurons [49,50].

Exposure to toluene, oral or by inhalation, results in psychomotor excitation, i.e. an effect similar to that induced

by ethanol and amphetamine. This effect may be prevented by blockade of DA D2 receptors or destruction of the dopaminergic projection in n.acc by 6-OHDA. It has also been shown that:

- toluene inhalation at high concentrations (11.000 ppm) results in an activation of DA neurons in VTA,
- perfusion of VTA slices with toluene (23–822 uM) results in an increased activity of DA and nonDA neurons. Similar effects were not observed in the areas beyond VTA, which suggests specificity.

Based on the above data, the authors conclude that toluene has the potential to directly activate DA neurons within the mesolimbic reward pathway [51–54]. It may be added that inhalation of toluene vapors stimulates DA release in the prefrontal cortex and increases the cocaine-induced DA release in n.acc [55].

Some data suggest that the activating effect of toluene on DA release may depend on the route of exposure. In experiments performed by Kondo et al. [56], intraperitoneal injection of 800 mg/kg of toluene failed to produce alterations in the concentration of DA or DA metabolites (DOPAC and HVA). It did, however, induce psychomotor activation, which suggests that depending on the route of entry, toluene may result in a DA-related and in a DA-unrelated effect on behavior.

As to the second question, studies on rats have shown long-lasting suppression of spontaneous activity of VTA DA neurons following chronic exposure to ethanol [57,58]. The behavioral response to systemic administration of amphetamine or cocaine [cited in 58,59], or local administration of DA into n.acc [60], is increased when the drugs are administered during the abstinence phase after chronic ethanol consumption. This effect may be related to a compensatory increase in the affinity or density of DA receptors in this area [58]. The cocaine-induced DA release in n.acc is increased after a short-term (6 days) repeated exposure to ethanol [61].

Little attention has been given so far to the possible long-term alterations within the DA system produced by exposure to industrial solvents. Two decades ago, Tilson et al. [62] reported that oral exposure of young rats to benzene resulted in long-term behavioral changes (increased spontaneous locomotor activity) possibly indicating long-term modulation of the DA system. Von Euler et al. [63,64] observed an increased behavioral response to apomorphine in rats weeks after a repeated low-level (80 ppm) exposure to toluene. An increase in the behavioral responsiveness to apomorphine (and increased binding to spiroperidol, DA D2 antagonist) was also observed after exposure to n-hexane and its metabolite, 2,5-hexanedione [65,66]. Quite recently, Beyer et al. [67] reported, for the first time as they claim, an increased behavioral responsiveness to cocaine in rats after a high-level exposure to toluene. In the opinion of these authors, the results support the supposition that exposure to volatile solvents may affect the subject's response to drugs of abuse and influence the likehood of using and/or abusing them. Beyer et al. [67] were mainly concerned about persons who use (and abuse) solvents for recreational purposes. However, their supposition also refers to persons exposed to these substances occupationally. Unfortunately, the existing information on this issue is extremely scanty. Some authors noted a more pronounced effects of amphetamine and cocaine in persons occupationally exposed to some solvents [68,69], which does not yet mean a more frequent psychostimulant (or other drugs) use by these persons. However, the almost anecdotal inclination of painters to abuse alcohol [70] is worth noting. To our best knowledge there are no studies concerning the abuse of psychostimulants or other drugs (opiates, cannabinoids) among persons occupationally exposed to solvents. Taking, however, into account prices of such drugs on the one hand, and usually poor social status of employees working under solvent exposure on the other, dependency on expensive drugs is rather unlikely.

The extramesencephalic groups of DA neurons

Groups A 12 and A 14: the tuberoinfundibular DA projection system

The tuberoinfundibular DA system (TIDA system) is implicated in the control of the pituitary function. DA facilitates the release of some hormones (gonadotropins, somatostatin) and inhibits the release of others (prolactin – PRL). The DA inhibitory control over the prolactin re-

lease is the most intensively investigated issue in the context of solvent exposure. According to some authors, the exposure-related increase in plasma PRL concentration provides evidence for a compromised DA function and may be regarded as a biomarker of exposure [7,71]. Such an effect was observed in workers exposed to styrene [72] and perchloroethylene [73]. In one study on styrene-exposed workers, the increase in plasma PRL concentration was accompanied by the reduced beta hydroxylase activity in blood [74,75]. It is worth noting that styrene concentrations at which these effects occurred were surprisingly low (about 25 ppm).

The physiological role of PRL is related predominantly to reproductive functions, although it also takes part in immunological processes and maintenance of homeostasis [76]. Several reports have demonstrated that reproductive functions may be affected in solvent-exposed workers, in both women (subfecundity, reduced fertility, spontaneous abortions, endometriosis) and men (infertility) [77–81]. In animal studies, changes in the hypothalamus suggesting an effect on the metabolism, release, and turnover of dopamine were found in rabbits after exposure to styrene, vinyltoluene, and ethylbenzene [74,82] as well as in rats and mice exposed to toluene [83–85] and benzene [86]. Although negative results were also reported, [87], the above observations indicate that exposure to at least some solvents may result in alterations of the functional state of the TIDA system and in physiological disturbances, which can be attributed to these alterations.

Group A 16: olfactory bulb

The existing data indicate that the DA neurons of the olfactory bulb take part in the reception and perception of olfactory stimuli as well as in memorization of olfactory information. It has been shown that stimulation of DA receptors suppresses synaptic transmission at the first relay between olfactory receptor neurons and mitral cells and that this depression is caused by activation of DA D2 receptors [88–90]. The most apparent evidence for the DA role in olfaction is the reduced ability to recognize and discriminate olfactory stimuli in the early, presymptomatic stage of idiopathic Parkinson's disease [91,92], i.e. the stage when the neuronal inclusions (Lewy bodies) characterizing this disease are present only in medulla oblongata and olfactory bulb neurons [93].

In most cases of occupational and nonoccupational exposure, the solvent enters the body through the respiratory system which makes the olfactory mucosa and olfactory receptors particularly exposed to these substances. It has been shown that the metabolites of some solvents may accumulate in the olfactory mucosa [94]. One may expect then that in the DA neurons of the A 16 group, harmful effects of solvents may be particularly well pronounced. Unfortunately, there are only a few reports dealing with this issue. In three of them, the authors report disturbances in olfactory functions in workers after long-term exposure to solvent mixtures [95–97]. In the summary, the authors conclude that their results "... suggest that solvents may cause nervous system dysfunction at lower levels than previously suspected, and that the olfactory system may be a critical target organ for the neurotoxic effects of solvents and other chemicals." [95]. No alterations in the olfactory function have been found in workers exposed for more than four years to styrene at low (10–60 ppm) concentration [98]. Whether olfactory deficits found in the three studies mentioned above were related to a dysfunction of A 16 DA neurons is an open question. A positive answer, however, is quite likely, considering the aforesaid functional relations between the olfactory receptors and the DA system.

A 17 group: retina

According to Djamgoz and Wagner "...DA has satisfied all the criteria for being a chemical messenger in the adult vertebrate retina". What is more, "...the evidence suggests that DA acts in retina as a modulator and as a transmitter." [99]. All types of retinal cells are sensitive to DA influence. It seems that DA is important for visual sensitivity, visual acuity and color discrimination. There are several papers indicating that occupational exposure to organic solvents may result in impairments of color vision (dischromatopsia) [100–104]. In the study carried out by Semple et al. [102], six solvents and their mixtures have been identified in the work environment: xylene, methyl ethyl ketone,

white spirit, 2-ethoxy ethanol, dichloromethane, and acetone. In a review paper by Gobba and Cavalleri [105], the following solvents were listed as potentially toxic for the visual system: styrene, perchloroethylene, toluene, carbon disulfide, n-hexane, and solvent mixtures. They emphasize that the disturbances in color vision may result from exposure at concentrations lower than the current occupational exposure limits proposed by the ACGIH. Studies on isolated retinas from rats exposed to styrene (300 ppm, 6h/day, 5 days/week for 12 weeks) have shown that exposure to styrene results in structural and functional alterations (neurodegeneration, DA depletion and GSH reduction) in amacrine cells [106]. On the one hand these results indicate that the DA system in the retina is vulnerable to styrene, on the other they suggest a possible mechanism of the damaging effect of this solvent on the visual functions.

CONCLUDING REMARKS

The paper presents a handful of data regarding the potential effects of solvent exposure on the DA system. It is by no means an exhaustive and systematic review of the existing knowledge of this issue. We hope, however, that the information included here is sufficient to show that exposure to solvents may influence the functions of each of the major groupings of DA neurons, leading to qualitatively discernible health effects. Other systems, particularly the GABAergic and glutamatergic ones, are also known to be susceptible to the solvent action [6]. Considering the interdependencies between neurotransmitter systems, it is obvious that functional alterations in the DA system following a solvent exposure may result not only from a direct toxicant interaction with cellular and subcellular components of this system, but also from its effects on other systems. For example, there is evidence that the activatory effect of ethanol on the DA system results, at least in part, from an inhibition (due to activation of GABA receptors) of GABAergic neuron activity in the substantia nigra pars reticulata [107]. It is quite likely that other volatile solvents may affect the DA system in a similar way [6]. Neurotransmitter systems are not the only ones that may be involved. A strong relationship was found for example between the DA system and the hypothalamo-pituitary-adrenal (HPA) axis [108]. Accordingly, activation of the HPA axis with a nonchemical stressor may induce long-term alterations in the DA system as efficiently as does exposure to DA agonists. Solvent odor may be a powerful stress-inducing stimulus, particularly for the laboratory rodents. In the rat, exposure to some solvents has been shown to stimulate the HPA axis and induce a specific EEG response identical with that induced by exposure to a predator odor [109–111]. Solvent odor may also be stressogenic to human subjects, especially to subjects well-informed about the exposure-related health risk. Unfortunately, this aspect of the toxicant's action on the exposed subjects attracts little attention of the scientific community.

Finally, we are not saying that the ability to influence the DA system, either directly or indirectly, is characteristic of all the substances classified as solvents. Certainly, of all the substances belonging to this group only a small proportion was tested for the effect on the DA system. In some experiments, changes suggesting alterations in the DA system were observed after exposure to some solvents but not after exposure to others [88,112]. It is worth stressing, however, that solvents with scientifically proven ability to affect the DA system are those, which belong to the group with the highest production and consumption volume (toluene, styrene, chlorethylene).

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