ORGANIC SOLVENTS AND TIME-DEPENDENT SENSITIZATION

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Key words: Multiple chemical sensitivity, Time-dependent sensitization, Organic solvents

Abstract. The nervous system is main target of the toxic action of most of organic solvents. There is little doubt that occupational solvent exposure may result in persisting neurobehavioural disturbances — the organic solvent syndrome. Recently, the solvents are quoted among possible causes of the abnormal condition referred to as multiple chemical sensitivity (MCS), and which is characterized by a psychosomatic overreactivity to a variety of chemicals present in food or ambient air. According to some authors, MCS is a manifestation of the time-dependent sensitization (TDS), a phenomenon of progressive increase in responsiveness to chemical agents following acute or intermittent exposure, and related to some functional aberrations within limbic structures. TDS is commonly induced by psychostimulant drugs. The purpose of the present paper was to show, based on the literature data, that under circumstances of acute and repeated exposure, some solvents (mainly toluene) exert effect on behaviour and on the functional state of some neurotransmitter systems similar to that exerted by drugs known to induce TDS. Of special importance is the fact that in case of solvents the behavioural and biochemical changes suggestive of sensitization appear after exposure at levels close to those admissible in the occupational exposure, and that the concentration-effect relationship is nonlinear (an inverted U curve). To date, however, only a few of the existing data may be regarded as a direct evidence of the solvent-induced TDS. It is mainly due to the fact that the experimental protocol of a TDS study does not match the experimental routine of neurotoxicity assessment. Some data suggest that some solvents are possibly unable to induce TDS. The necessity to assess the commonly used solvents for their ability to induce TDS has been emphasized.

The risk of long-term health consequences resulting from occupational and environmental exposure to toxic chemicals is nowadays a problem of great concern for occupational medicine and for the regulatory agencies. Volatile organic solvents occupy the top of the list of such chemicals due to their production volume, multitude of occupational and nonoccupational applications, the route of entry into the organism and the easiness of absorption and tissue penetration.
The primary place of toxic action of organic solvents, typically aliphatic and aromatic hydrocarbons, is the central nervous system (CNS). Some epidemiological studies and case reports suggest that occupational exposure to these compounds may result in persistent neurobehavioural impairments, referred to as 'organic solvent syndrome' (OSS). Consequently, in some countries OSS has been acknowledged as an occupational disease (39,56). For some time now, solvents have been also mentioned as suspected aetiologic factors in multiple chemical sensitivity (MCS), an illness with incidence which, in some highly developed countries, has alarmingly increased (8,38).

MCS is a chronic condition which is manifested by the occurrence of a symptom complex after exposure to a variety of chemicals present in food or ambient air at concentrations which, according to our current knowledge, should produce no harmful effects. The development of MCS is a two-stage process: initiation by an acute, high-level exposure or repeated low-level exposure to a chemical, and elicitation of symptoms by the same substance or a variety of other related and unrelated chemicals (Fig. 1). The symptom variability is very high. Usually, symptoms suggestive of an involvement of the central nervous system dominate. They include concentration-attention and memory failure, fatigue, tiredness, depression, dizziness, somnolence during day hours, derealization, irritability and anxiety. Somatic symptoms, such as muscle and joint pains, digestive problems, weakness, headaches, sinusitis and nasal allergies are also common (7,11).

Stage I: Initiation

- Acute high-level or repeated low-level exposure
- Activation of limbic system structures
- Organism's response (somatic, autonomic, endocrine)

Stage II: Elicitation

- Low-level chemical exposure
- Exposure initiated progressive increase in limbic system reactivity
- Increased activation of limbic system structures
- Increased organism's response (somatic, autonomic, endocrine)

Fig 1. Two-stage process in the development of multiple chemical sensitivity. The arrows do not refer to any known neuronal pathway but denote the succession of events. At stage I, an acute high level or repeated low-level exposure to a chemical results in a direct or indirect activation of limbic system structures. Limbic system activation prompts the appearance of somatic, autonomic and endocrine response (symptoms) and initiates the process of a gradual increase in the limbic system reactivity (a kindling-like phenomenon). Owing to that, at stage II a low-level exposure to a chemical induces a disproportionally large response (7).
The involvement of solvent exposure in the MCS aetiology is suggested by the medical histories (self reports) of patients with MCS diagnosis. According to Miller and Mitzel, for example, 75 out of 112 MCS patients attributed the beginning of their illness to remodelling of a building which commonly involves exposures to mixtures of solvents released from fresh lacquers, paints and glues (40). Besides, some authors found that over 50% solvent-exposed industrial workers manifested symptoms of illness in the presence of a chemical odour (42,50).

The increasing prevalence of the MCS cases raises concern not only among medical personnel but also among toxicologists (mainly neurotoxicologists) and regulators responsible for setting hygiene standards (occupational and environmental exposure limits). As already mentioned, in the MCS patients symptoms of disabling severity may be triggered by exposure levels which, according to the existing standards, should produce no harmful effects. Thus, either the symptoms result from an action of additional exposure-related factor, or some important aspects of the toxic action of a given substance have been overlooked, and not taken into account while testing its toxicity and, consequently, setting the standards of exposure. According to some authors, the symptoms in MCS patients are being triggered by fear of possible harmful effects of exposure rather than by the exposure itself. According to others, MCS may be explained in terms of the Pavlovian conditioning. In the latter case, MCS may be regarded as a result of the association between the odour or taste of a chemical substance and an aversive state which may, but not necessarily, be induced by this substance (10,51). Another hypothesis claims that MCS is a manifestation of time-dependent sensitization (TDS) of limbic structures and pathways responsible for regulation of attention/memory affect viscera and endocrine functions (7,54). TDS is related with the phenomenon of the progressive increase in responsiveness to a variety of stimuli after an acute or repeated, intermittent exposure to a chemical, pharmacological, physical or psychological stressor (3,5,52).

Numerous experimental studies have confirmed that TDS can be induced by the systemic or central administration of variety of drugs (9). The question is whether exposure to a solvent (or solvents) can sensitize the subject — at the neuronal and behavioural levels — to other chemical stressors including the solvent itself. The existing data from experimental animal studies and some clinical observations make this possibility a likely one.

Most of the existing experimental data on TDS come from research into psychostimulants, mainly amphetamine. On the other hand, the majority of the experimental animal studies of solvent neurotoxicity concerns toluene, a representative of aromatic hydrocarbons which are common constituents of industrial solvent mixtures. There are important similarities between the neurobehavioural effects of amphetamine and toluene which explains why toluene, like amphetamine, is the substance of abuse. In the adult rat, the most evident behavioural response to a low dose (up to 2 mg/kg) of amphetamine is an increase in locomotion (36,49). The same effect is produced by toluene, and several other solvents (12,17), administered systemically at low doses or in the course of a low-level inhalation exposure. Moreover, like amphetamine, toluene possess rewarding properties (62), and affects behavioural performance in some test situations much in the same way as amphetamine does (18). At high doses, however, acute effects of toluene and other volatile organic solvents differ markedly from those produced by amphetamine.
Whereas the former produces behavioural depression and narcosis (24, 63), the latter produces stereotypes (49), a behaviour regarded by some authors as a way of coping with excessive excitation (41).

The psychostimulant effect of amphetamine is commonly linked with the influence of this drug on the catecholaminergic systems. Apart from being a monoamine oxidase (MAO) inhibitor, amphetamine prompts the release of dopamine from dopaminergic terminals (28).

The locomotion-stimulating effect of this drug is due to an enhanced dopaminergic transmission in the striatum (13, 31). It has been demonstrated in numerous studies that exposure to organic solvents affects functioning of the catecholaminergic systems especially the dopaminergic one (Table 1). Generally, the data suggest an increased dopaminergic activity during the exposure to solvents which might account for the locomotion stimulating phase in the effect of such an exposure. Surprisingly, Kondo et al. (33) found that intraperitoneal injection of 800 mg/kg toluene, while producing a significant increase in locomotor activity, did not affect the extracellular levels of dopamine and its metabolites. It was in contrast to methamphetamine (1.0 mg/kg) which stimulated locomotion and increased the extracellular dopamine level. However, it has recently been found that in the presence of remoxipride, a selective D2-dopamine antagonist, toluene-induced hyperactivity was reduced by more than 50% (47). According to the authors, their results clearly show that toluene induces locomotor hyperactivity through a dopamine-dependent mechanism.

It appears from the above data, that toluene, and possibly other volatile solvents, are able to activate the dopaminergic system, i.e. the same system which is being activated by the psychostimulant amphetamine. Activation of the dopaminergic system plays a crucial role in the triggering the sensitization process (30, 52, 57).

In the studies of TDS, the experimental procedure consists in a pretreatment of animals once or, more commonly, repeatedly over several days with a dose of the substance under study and then, after an interval of several days or weeks, testing the animal behavioural response to a challenge dose of the same substance, or another stressor (to test cross-sensitization). Sensitization is said to occur when the behavioural response to the pharmacological challenge is higher in the animals pretreated with the studied chemical than in the animals pretreated with the vehicle. Such an increased response is a typical outcome of pretreatment with psychostimulants like amphetamine or cocaine (49). In many instances cross-sensitization was reported: animals pretreated with a psychostimulant showed an increased behavioural response to other pharmacological or physical stressors (3, 4). The neuronal background of TDS is not well understood (52). Nevertheless, there seems to be a general agreement that the psychostimulant-induced sensitization is a form of neuronal adaptive response to a transient dopaminergic overstimulation, and that the net result of these adaptations is a long-lasting increase in dopaminergic sensitivity. This increase was ascribed to a persistent facilitation of the psychostimulant-induced dopamine outflow from dopaminergic endings in the caudate and nucleus accumbens, or an increased responsiveness of striatal dopaminergic receptors (30, 34). There is some evidence showing that at the behavioural, and possibly neural levels, exposure to solvents is able to produce effects similar to those mentioned above. In a series of experiments, von Euler et al. have shown that in
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Rats tested 16–18 days after a four-week (6 h/day, 5 days/week) low-level (80 ppm) inhalation exposure to toluene, the locomotor response to apomorphine, a direct dopaminergic agonist, was markedly increased (59,60). This result may be regarded as an example of cross-sensitization and the repeated low-level solvent exposure as the sensitizing agent. Of special significance is the fact that it was produced by a concentration of toluene close to the TLV-TWA value recommended for this hydrocarbon (1). An effect similar to that of toluene was also observed in rats treated with 3 ethanol in drinking water for 8 weeks; in these rats the amphetamine-induced locomotor hyperactivity was significantly higher than in the control animals (37). It seems likely that effects similar to those mentioned above may be also produced by exposure to other solvents. Some time ago we studied the long-term behavioural effects of an inhalation exposure to trimethylbenzene isomers: pseudocumene (1,2,4-trimethylbenzene) or hemimellitene (1,2,3-trimethylbenzene) each at the concentration of 0, 25, 100 or 250 ppm. Exposure duration conditions were the same as in von Euler’s (59,60) experiments on toluene (6 h/day, 5 days/week for 4 weeks). The behavioural testing started on day 14 and continued till day 60 after the last exposure. It included assessment of short term spatial memory in the radial maze, open-field behaviour, passive and active avoidance learning and hot-plate behaviour. Differences between the exposed and nonexposed rats were found in all test situations except for the radial maze. The exposed rats were slightly hyperactive in the open field, performed worse in the passive and active avoidance situation, and showed stronger and more persistent footshock-induced emotional response. Generally speaking, the results suggest that a decreased ability to inhibit locomotor response in stress-inducing environmental context might constitute the primary cause of the observed behavioural disturbances in the exposed rats (19,61).

It has been demonstrated in several studies that a repeated administration of amphetamine or other dopaminergic system-activating drugs sensitizes animals to behavioural effects of footshock i.e. they show an exaggerated locomotor response to this stimulus (4,20,21,29,30,53). The character of behavioural alterations seen in our rats suggests that we were dealing with the same phenomenon; sensitization to the footshock stress, which, in our case, resulted from repeated exposure to trimethylbenzene.

As mentioned above, the neuronal adaptations subserving sensitization induced by psychostimulants are ascribed to some persisting changes in the functional state of the dopaminergic system. The available literature data show that long-term, if not permanent, changes within this system may also develop as a consequence of solvent exposure. The results of von Euler’s studies on the binding parameters of the dopamine agonists, suggest that a four-week exposure to toluene at 80 ppm results in a persistent increase in the number of dopamine D2 receptors in the rat neostriatum (60). In another study (23), rats were exposed to toluene (40–320 ppm; 4 weeks, 6 h/day, 5 days/week) and tested after a postexposure period of 29–40 days. The obtained results suggest that exposure to toluene at 80 ppm or less leads to persistent increase in the affinity of dopamine D2 agonist binding in the rat caudate-putamen. Interestingly, no similar changes were observed in rats exposed to xylene or styrene. An increase in dopamine (and other biogenic amine) concentration was found in the hypothalamus, midbrain and medulla oblongata of mice after a 28-day exposure to toluene or benzene in drinking water (25,26). Changes in dopaminergic system which may be related to solvent exposure were
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NA — noradrenaline; DA — dopamine; PET — positron emission tomography
also found in humans. In a recent paper, Edling et al. (16) have presented results (of studies with the use of positron emission tomography) suggestive of an increased dopamine synthesis in brains of patients with neuropsychiatric symptoms due to occupational solvent exposure. According to the authors, 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.

Of importance is the fact that in the Hillefors-Berglund et al. studies, the concentration-effect relationship was nonlinear; of several concentrations of toluene tested, the highest appeared less effective in inducing the increase in the extracellular dopamine than the lower ones (23). A similar nonlinearity was also found in our behavioural studies on trimethylbenzene mentioned above (19); for both (pseudocumene or hemimellitene) isomers the behavioural alterations detected after exposure to 250 ppm were considerably less evident than those found after exposure to 100 (pseudocumene) or even 25 ppm (hemimellitene). The above might suggest that at higher exposure levels, another counterbalancing process, which is leading to persistent changes in the dopaminergic system and behavioural alterations, is also being activated. As a result, the net effect of a high-level exposure is less evident than that observed at lower exposure levels.

To sum up, the above data seem to support the conjecture that exposure to organic solvents, or at least some of them, may initiate TDS, a process which makes the subject hypersensitive to pharmacological and environmental stressors. Like in the case of psychostimulants, this effect is likely to be somehow related to persistent changes in the functional state of the dopaminergic system. Of special importance is the fact that changes within the dopaminergic system and behavioural alterations were found after exposure to solvents at concentrations approaching those recommended for occupational exposure and that the concentration-effect relationship was nonlinear; low concentrations appeared more efficient than the highest ones in producing changes in the dopaminergic system (23) as well as in behaviour (19,61). Bell has noted that, in some cases sensitization occurs when the substance is administered at low doses. High doses do not induce sensitization and even may reverse the process induced by exposure to low doses (7). The efficiency of low-level solvent exposure in inducing persistent behavioural and neurochemical changes, as well as the nonlinearity in the concentration-effect relationship may pose serious problems for those involved in setting occupational and environmental standards of exposure. Therefore, more data on the presumed sensitizing properties of solvents are urgently needed.

As suggested by Antelman et al. (6), the most important factor in triggering TDS by a chemical is its foreignness and stressfullines to the organism rather than any specific pharmacological property. A solvent, like many other substances assessed experimentally for neurotoxicity, is almost always foreign and always stressful (due to its odour) for the experimental subjects (usually rats), and as such, it should be able to trigger TDS. It is not quite certain, however, that pharmacological properties of the substance under study do not matter. For example, sensitization by repeated treatment with methamphetamine appear to be preventable by scopolamine or clonazepam, and, neither scopolamine, nor clonazepam produced sensitization when given alone (27,45). The above contradicts Antelman's suggestion and shows that pharmacological properties of a substance may consist important factors in
triggering the sensitization process and, possibly, determining its behavioural outcome. As far as organic solvents are concerned, any data from a study aimed at detecting and comparing the sensitizing properties of different solvents have not yet been published. The results obtained by von Euler et al. (59,60) show that such properties characterize toluene. However, in experiments carried out by Hillefors-Berglund et al., changes in the dopaminergic system similar to those produced by exposure to toluene, were not observed after exposure to xylene or styrene which may suggest that the latter two solvents differ from toluene in the sensitization potential (23). It should be established therefore, in specially designed studies, whether exposure to other common organic solvents can sensitize the exposed subjects to these solvents and to other chemical or physical stressors. Data obtained in these studies might be of help in assessing the risk of sensitization induction, and by the same of MCS, associated with exposure to a given solvent.

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Received for publication: August 4, 1999
Approved for publication: November 16, 1999