NEUROTOXICOLOGY OF CHEMICALS

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Introduction

Neurotoxicology is relatively a new discipline of toxicology, though adverse effects of preparations used in ayurveda and unani system of medicine have been described in ancient Indian literature. The known and suspected causes of brain related disorders include exposure to chemicals e.g. therapeutic drugs, substances of abuse, food additives, food products, cosmetic ingredients, natural constituents of plants and bacteria, pesticides, metals, etc. Industrial chemicals such as lead, manganese, mercury and agricultural chemicals such as pesticides and herbicides and several others have been implicated in learning, memory disturbances and diseases like Parkinson's, Alzheimer's, attention deficiency syndrome and others.

Neurotoxicants pose an insidious threat to human health; the severities of symptoms vary with the intensity of exposure from headache to drowsiness on mild exposures and widespread neurological impairment upon high exposures, which may lead to coma and death.

The subject of Neurotoxicology has been of significant interest and some outstanding contributions have been made from India.and a number of.institutions all over the country are working in the field of Neurotoxicology. The major contributions have been made by Indian Institute of Toxicology Research (IITR, earlier known as Industrial Toxicology Research Centre), Lucknow, National Institute of Mental Health and Neuro-Sciences (NIMHANS), Bangalore, National Brain Research Centre (NBRC), Manesar, Jiwaji University, Gwalior and Jamia Hamdard, New Delhi. During the last two decades the subject has received considerable significance as evident from the number of symposia, seminars and updates on neurotoxicology organized by various institutions in the country. In almost all annual conferences of the Indian Academy of Neurosciences and other neuroscience related societies, the topic of neurotoxicity has been a major subject of discussion.

The thrust has been to delineate the basic mechanisms of neurotoxicity of various chemicals using biochemical, pharmacological, pathological and modern biological tools; study distribution of the chemicals in brain and the enzymes and biological molecules and receptors through which they act and enzyme system by which they are metabolized in brain.. Efforts have also been made to understand the factors influencing the neurotoxicity. Some studies have been made on protection of the neurotoxic effects using plant extracts and antioxidants, but are confined to experimental studies. The agents studied are drugs, metals, pesticides, solvents, plant products and natural toxins.

Malnutrition is an important predisposing factor, particularly protein and iron deficiency (Khanna et al. 1988, 1991, 1992, 1994, Mohindra et al. 1990, Adhami et al. 1996), in the neurobehavioral toxicity of environmental chemicals.

The lipophilic nature of many chemicals such as organic solvents and organochlorine compounds leads to accumulation in tissues with a high lipid content, thus making brain and nerves potential depots for these compounds and their metabolites. Role of cytochrome P450s (Cyp450) in the etiopathogenesis of several of the neurodegenerative disorders induced by drugs and environmental toxins have been indicated in recent years. The possibility that inhalation of organic solvents (acetone, isopropanol, n-hexane, etc) found commonly in the workplace that induce P450 2E1 in the liver, may also induce this enzyme in the brain and increase the risk of neuronal damage due to the generation of free radicals. (Parmar et al, 2004).

The recent reports that subpopulations of humans such as children and the elderly may be differentially sensitive to exposure to neurotoxic agents has aroused a great concern about the outcome of exposure at low doses and prolonged periods.

Children are especially vulnerable to adverse health effects right before and after birth, when they are passing through the most rapid phases of development. A few industrial chemicals (e.g., lead, methyl mercury, polychlorinated biphenyls [PCBs], arsenic, and toluene) are recognized causes of neurodevelopmental disorders and subclinical brain dysfunction. Exposure to these chemicals during early fetal development can cause brain injury at doses much lower than those affecting adult brains. About 200 chemicals are known to cause clinical neurotoxic effects in adults; many additional chemicals have been shown to be neurotoxic in laboratory models. Developmental neurobehavioral toxicity studies have been undertaken on animal models at different periods of development (pre- and postnatal) to assess the potential of neurobehavioral toxicity of these environmental chemicals (Zaidi et al. 1985a, b,c; Husain et al. 1987).

Neurotoxicants can cross the placenta from mother to child, enter the baby's brain and damage it permanently. The consequences are loss of intelligence (as measured by IQ), behavior disruption, increased risk of attention deficit disorder and heightened risk of autism. Many of these effects can last a lifetime. Recognition of these risks has led to evidence-based programmes of prevention, such as elimination of lead additives in petrol. Biomarkers can serve the purpose of confirmation of diagnosis, monitoring treatment effects, and prediction of clinical outcomes for example, circulating plasma acetylcholine esterase (AChE) activity can serve as a good biochemical marker of organophosphates and of other environmental contamination due to neurotoxic substances (Gaitonde et al. 2006).

Experimental studies on specific parameters involving behavioral, neurochemical and immunohistochemical approaches have been used to understand the behavioral alterations in animals and neuronal modifications at the tissue and

cellular level. Both *in vivo* and *in vitro* studies using animal model and cell cultures respectively have been carried out at tissue and cellular levels to investigate mechanisms underlying neurotoxicity of environmental contaminants including metals (manganese, cadmium, lead and aluminum) (Agrawal et al 1986, Kumar et al. 1996 a,b, Adhami et al. 2000, pesticides such as endosulfan, lindane, BHC, synthetic pyrethroids, and organophosphates (Anand et al. 1986, 1987, 1990, 1998, Aziz et al. 2001, Dayal et al. 2001, 2003, Husain et al. 1991, Malviya et al. 1993, 1994, 1996, Parmar et al. 2003, (Srikanth and Seth 1989, 1990), Seth and Chandra 1988, (Seth et al. 1986), solvents (n-hexane, trichloroethylene) (Agrawal et al. 1985, Subramoniam et al. 1989), and plastic monomers—acrylamide, styrene, styrene oxide and dibutyl tin dilaurate, acrylonitrile and methyl methacrylate (Alam et al. 1988, 1993, Khaliq et al. 1991, Husain et al 1985a,b,c, 1986,1989, Zaidi et al. 1985a, Subramoniam et al 1991, Srivastava and Seth 1985, Srivastava et al. 1986). Human and rat platelets demonstrating similar pharmacological responsiveness as brain have shown the presence of binding sites for dopamine and serotonin receptors (Khanna et al 1987 a, b). Parallel response on the binding of 3H-Spiperone and 3H-5-HT in rat platelets and brain was observed while studying interaction of selected neurotoxicants (Khanna et al. 1987 c, Husain et al. 2001) suggesting that platelets could be used as a peripheral model for central nervous system. An in vitro test system has been developed and validated using neuronal cell lines (PC12) to study the mechanism of chemical neurotoxicity at cellular level. The battery of tests developed with these cell lines were successfully used to study free radical mediated toxicity, response of stress activated genes (c-fos, c-jun and GAP-43) that involve second messenger pathways (Ca2+, PKC) in neurotoxicity of chemicals (Siddiqui et al. 2008 a, b).

Most toxic polyneuropathies encountered in routine clinical practice are due to iatrogenic pharmaceutical intoxications. The majority (and unfortunately the most difficult) of the cases of toxic polyneuropathies are individual intoxications due to small-scale, often chance occupational exposure, and also due to intentional, suicidal ingestion. The exception to the above rule involves endemic exposure, such as arsenic in West Bengal (Mukherjee et al. 2003, 2005).

A detailed review on the status of neurotoxicology in India has been published by Misra (1989), replete with ancient Indian neurotoxicology covering the entire scenario from Ayurvedic and Unani systems of medicines up to modern research. This article presents R&D contributions made in India in the area of neurotoxicology during the last two decades only with possible directions for future research. The most common substances with neurotoxic potential, which include environmental and occupational chemicals, have been considered, for example heavy metals, pesticides, organic solvents and alcohol, also several vegetable and animal poisons. In spite of sincere efforts of the authors to include all major contributions, some omissions may have been there but these are not deliberate.

Metals

Chronic exposure to toxic metals usually goes undetected and unchecked in families from developing countries because people are unaware of the dangers and there are no effective national policies to prevent and control exposure. The chronic and acute manifestations and behavioral deviations on exposure at low dose levels to toxic metals are known. In relevant occupations, exposure to toxic metals by inhalation, dermal absorption and ingestion cause behavioral changes. By cumulative action, they lead to neurotoxicity and influence circadian rhythm and sleep patterns (Venkatakrishna-Bhatt & Panchal, 2001; Sethi et al, 2006). Inorganic lead (Pb^{++}) can damage both the central nervous system (CNS) and peripheral nerves and cause disturbed memory, and encephalopathy. Manganese (Mn^{++}) causes earlier functional changes in basal ganglia which produce a Parkinsonian-type symptomatology. Similarly, zinc (Zn^{++}) and cadmium (Cd^{++}) are implicated with CNS effects either in the depression or excitation. Recently heavy metal mediated toxicity has been linked to diseases such as, Alzheimer's, Parkinson's, autism, lupus, and amyotrophic lateral sclerosis. These toxic metals have been found to have synergistic negative effects on childhood development and cognitive ability. In a recent study (Jadhav et al, 2007) involving sub-chronic exposure via drinking water to low doses of a mixture of metals (arsenic, cadmium, lead, mercury, chromium, manganese, iron, and nickel), it was observed that general health of male rats was affected and combined exposure of Pb, Mn and Cd enhanced accumulation of all three metals in the brain (Shukla & Chandra,1987).

Current approved treatment lies in the administration of chelating agents that forms an insoluble complex with the metal and removes it. They have been used clinically as antidotes for treating acute and chronic poisoning. One of the important approaches has been the use of combination therapy. This includes use of structurally different chelators or a combination of an adjuvant/ antioxidant/ herbal extracts and a chelator to provide better recovery. A number of other strategies based on laboratory animal studies have been suggested by Flora et al, (2007a).

Lead

The primary target for lead toxicity is the nervous system, both in adults and children. Long-term exposure of adults to Pb at work has resulted in decreased performance in some tests that measure functions of the nervous system. Chronic low-level Pb exposure causes growth retardation and intellectual impairment. Cognitive dysfunction, growth retardation, hyperactivity and neurochemical deficits in animals and humans have also been reported. Occupational exposure to Pb was studied among silver jewellery workers (Kachru et al, 1989). Levels of Pb in hair were taken as a reference of exposure among printing press workers (Sinha et al. 1993) and their psychomotor, visuomotor and vigilance performance was studied for neurotoxic effects. Lead exposure among three wheeler drivers, battery reconditioner workers and jewellery makers was found to affect the immune system

(Mishra et el. 2003) Earlier, tooth lead content of few residents of Agra was taken as an indicator of environmental lead pollution (Srivastava et al. 1992).

Pre-and perinatal exposure to lead is reported to retard mental development and result in to lower intelligence in childhood and such effects may persist beyond childhood. A cross sectional study undertaken by Kalra et al. (2003) showed higher blood level in school children residing in areas close to vehicular traffic. Developing brain has been found to be more susceptible to the neurotoxic effects of Pb as observed by a decreased AChE activity in cerebellum and hippocampus of developing rat brain (Reddy et al, 2003). A preliminary investigation was carried out in a hospital in Lucknow, India, to study the range of Pb exposure in pregnant women and fetuses (Saxena et al, 1994). A correlation between high Pb levels and various socio-environmental factors was derived; nevertheless, a need for regular monitoring and lowering of environmental Pb exposure is required.

Among the factors influencing the lead toxicity, alcohol plays an important role. Prolonged and heavy consumption of alcohol may increase the toxicity of Pb (Tandon & Flora, 1989; Flora et al, 1999; Verma et al, 2005). Concurrent exposures of two metals, Pb and Mn may be responsible for the disruption of nerve impulse transmission as observed in rats (Hussain et al, 1987).

Oxidative stress is considered a possible molecular mechanism involved in Pb neurotoxicity. Some of the neurotoxic effects of Pb have been reported to be mediated by apoptosis, which on pretreatment with 17-B-estradiol (Chetty et al. 2007) or melatonin (Suresh et al, 2006) can be prevented. Ca2+ or Zn2+ supplementation significantly reversed the Pb-induced perturbations both in the levels of monoamines and in the activity of monoamine oxidase (MAO) in all the brain regions of mice (Prasanthi et al, 2005) in a dose dependant manner (Devi et al, 2005). However, the recovery in monoamine levels and MAO activity was more pronounced with Ca2+ supplementation as compared to Zn2+, proving that dietary Ca2+ and/or Zn2+ provide protection against Pb-induced neurotoxic effects. Thiol-antioxidant supplementation following Pb exposure may also enhance the reductive status of brain regions by arresting the lipid peroxidative damage in these regions (Nehru & Kanwar, 2004). Usefulness of curcumin in preventing Pb-induced neurotoxicity has been suggested as simultaneous treatment with Pb, curcumin was found to increase the activity of antioxidant enzymes superoxide dismutase (SOD), catalase (CAT) and reduce levels of glutathione (GSH) levels in rat brain regions (Shukla et al, 2003).

Pb administration (20 mg/kg body wt for 8 wk) also showed degenerative changes in the cerebral cortex with a marked decrease in DNA, RNA, and protein content. Whereas during concomitant administration of Pb and Se, only marginal changes were observed, there was significant improvement in values of DNA and RNA content (Nehru et al, 1997); a significant improvement in activity of AChE and MAO was also seen (Nehru & Dua, 1997).

Significant changes, rather selective modulation, have been observed in neuronal nitric oxide synthase (nNOS) in the developing rat brain following perinatal Pb-exposure (Chetty et al. 2001; Reddy et al, 2002) but no effect on the heme oxygenase activity was reported (Reddy et al, 2002). A linear correlation exists between increase in lipid peroxidation and decrease in AChE activity (Sandhir et al, 1994) showing that Pb may exert its neurotoxic effects via peroxidative damage to the membranes.

Selective effects on cholinergic system in brain areas controlling learning and cognitive behavior (cerebellum and hippocampus) have been reported by Reddy et al (2003, 2007) even after withdrawal of Pb exposure. *In vitro* and *in vivo* studies on Pb using rat brain revealed an enhancement in the biological activity of calmodulin (Sandhir and Gill 1994a), alteration in calcium homeostasis with a decrease in intracellular levels of cAMP (Sandhir and Gill 1994b, c), and calcium calmodulin neurotransmitter release associated with behavioral impairment (Gill et al. 2003). Sub chronic exposure to low levels of Pb resulted in significant decrease in dopamine (DA) content, attenuation of stimulus-induced release of DA in the dopaminergic projection area of nucleus accumbens (NA), and alterations in tyrosine hydroxylase (TH) activity in NA and frontal cortex of rat brain (Jadhav & Ramesh, 1997; Ramesh & Jadhav, 1998).

Cadmium

A toxic heavy metal, cadmium, is well known for its occupational health risk and its behavioural and neurotoxic effects have been well documented. Inhalation of cadmium fumes or dust is the primary cause of cadmium exposure. Contamination of ground water (wells) and food are the other predominant sources of environmental pollution (Srikant et al, 1994; Sethi et al, 2006). There are reports of cadmium-induced polyneuropathy and neuropsychiatric manifestations (Sethi et al, 2006). A number of experimental studies also have related Cd with neurotoxicity. Chronic Cd exposure in rats resulted in a general depression in gross locomotor activity and exaggerated emotional reactivity in the behavioral expression (Ali et al, 1990). Morphological changes were reported in developing as well as adult rats (Murthy et al, 1987), there was an age difference in the accumulation of Cd and 5-hydroxytryptamine (5-HT) turnover in brain regions; the accumulation of Cd in all the brain regions was significantly more marked in growing rats compared to adults after identical exposure (Gupta et al, 1990). Peripheral neurotoxicity was demonstrated in growing rats by Murthy et al (1991). Cadmium, may directly/indirectly through inhibition of superoxide dismutase (SOD) affect lipid peroxidation (LPO) and damage the associated physiological functions (Shukla et al, 1987a; b; Gulati et al, 1986, 1987) leading to central nervous dysfunctions. *In utero* exposure to Cd may retard the development of certain neurochemicals which could have long term implications on the brain functions (Gupta et al, 1991). Neurotoxicity of Cd is oxidative stress-mediated (Kumar et al, 1996 b); inhibition of glutathione peroxidase and catalase was reported in various brain regions (Shukla

et al, 1989) on Cd exposure at different time intervals. Treatment with antioxidant substances (vitamin E and/or selenium) was found to inhibit cadmium induced neurotoxicity (Shukla et al, 1988 a; b, c; Srivastava & Chandra, 1989). Alcohol exacerbates the effects of Cd toxicity showing significant accumulation of Cd with elevation of 5-HT in medulla oblongata and alters monoamine oxidase (MAO) and norepinephrine (NE) activities on chronic exposure (Murthy et al, 1989).

Cd was found to inhibit brain calmodulin both in vitro and in vivo (Vig et al. 1989) and stimulate lipid metabolism (Gulati et al. 1986, 1987). Co-exposure to ethanol and Cd resulted in enhanced oxidative stress and greater accumulation of the metal in brain regions of rats (Pal et al 1993 a, b). Under nutrition in rats enhanced neurotoxic effects of cadmium (Gill et al. 1989).

Mercury

The easy access of mercury through multiple pathways air, water, food, cosmetic products and even drugs increase the exposure to man, particularly in low doses (Zahir et al, 2005). Fetus and children are more susceptible towards mercury toxicity. Decreased performance in areas of motor function and memory has been reported among children exposed to presumably safe mercury levels. Similarly, disruption of attention, fine motor function and verbal memory was also found in adults on exposure to low mercury levels. It is an occupational hazard for dental staff, chloralkali factory workers and gold miners, etc.

Methyl Mercury has been reported to decrease the dopamine receptor binding in brain and platelets of rat.(Seth and Seth (1989) and reduce the motor and memeory function (zahir et el. 2006) In aquatic environments, inorganic mercury is microbiologically transformed into lipophilic methylmercury which makes it more prone to biomagnification in food chains. Consequently, populations with traditionally high dietary intake of food originating from fresh or marine environment have highest dietary exposure to mercury. Methyl mercury is among the most potent neurotoxicants. Children are exposed when their mothers eat mercury-contaminated fish during or before pregnancy. Although no reports on the methyl lmercury poisoning are available form India, its presence has been reported in water (Pandit et el. 1997) For the treatment of mercury poisoning efficacy of DL-alpha-lipoic acid during various modes of therapy, on the antioxidant status was established (Anuradha & Varalakshmi, 1999).

Arsenic

Arsenic, like most of the other metals has been found in studies associated with neurologic, vascular, dermatologic, immune, endocrine (diabetes) and carcinogenic effects along with reproductive disorders (Mazumder, 2003; Chowdhury et al, 2000; Mahata et al, 2004, Majumder, 2004; Singh et al, 2007) and affects more people than any other toxic substance. Long-term exposure to ingested arsenic has been documented to induce peripheral vascular disease, carotid

arteriosclerosis, ischemic heart disease, and cerebral infarction in a dose-response relationship (Mandal et al, 1997). Arsenical neuropathy and adverse obstetric outcome were observed, indicating severity of exposure (Ahamed et al, 2006). The range of arsenic concentrations in hair, nail and urine was 137-10,900; 764-19,700 ug/kg, and 23-4,030 ug/L, respectively which correlated significantly (r=0.76, 0.61, and 0.55, respectively) with drinking water arsenic concentrations. The diagnosis of subclinical arsenicosis was made in 57%, 83%, and 89% of hair, nail, and urine samples, respectively in West Bengal (Rahman et al, 2001). In the study, approximately 90% of children below 11 years of age living in the affected areas showed hair and nail arsenic above the normal level. Children appear to have a higher body burden than adults despite fewer dermatological manifestations. The similarity to previous studies exhibiting arsenic-typical neuropathy due to arsenic contamination in West Bengal (Rahman et al, 2001; Mukherjee et al; 2005), with 63% of the adults in a study in Bihar (Chakraborti et al, 2003) and U.P. (Ahamed et al. 2006) indicates that people from a significant part of the surveyed areas (upper, middle, and lower Gangetic plains) were suffering from arsenic toxicity. The magnitude of severity was related to the concentration of arsenic in water as well as duration of the exposure. Chronic arsenic toxicity due to drinking of arsenic contaminated water causes significant morbidity in children in different parts of the world (Mazumder, 2007). Epidemiological studies on arsenic contamination in drinking water indicated presence of arsenic in fetal tissues.

Chronic exposure to arsenic in developing and adult rats has been found to alter levels of GABA, glutamate and biogenic amines in brain regions (Nagaraja and Desiraju 1993) and cause a decrease in the activity of brain AChE associated with impaired learned behavior (Nagaraja and Desiraju 1994).

Arsenic induced free radical toxicity was shown experimentally in mice (Rao & Avani, 2004). Experiments on human fetal brain explants on exposure to arsenic in culture showed disturbance in lipid peroxidation, generation of nitric oxide (NO), reactive oxygen species (ROS) and apoptosis (Chattopadhyay et al, 2002). The oxidative stress challenged by antioxidant vitamins C, E or chelator dimercaptosuccinic acid (DMSA) showed partial protection from arsenic toxicity. Combined administration of selenium and meso-2,3 – dimercaptosuccinic acid reduced arsenic induced oxidative stress in brain although it had no beneficial effect on arsenic depletion (Modi et al. 2008).

Aluminum

Based on extensive literature (Gupta et al, 2005) it is concluded that, the neurotoxic effects of aluminum are beyond any doubt and this environmentally abundant non-redox trivalent cation has also long been implicated in the pathogenesis of Alzheimer's disease (AD). It may also be important in the etiopathogenesis of a specific motor neuron disease (Sood et al. 1990). However, the definite mechanism of aluminum toxicity in AD is not known. Aluminum-amino

acid complexes play an important role in the complex biology of the metal; a mechanism of Al-D-Asp binding and its ability to modulate DNA topology has been proposed (Bharathi et al;2003) with the help of computer modeling, gel studies, and ethidium bromide binding. Aluminum was found to alter glutamate and gamma-amino butyrate levels as well as activities of associated enzymes with regional specificity. Protein malnutrition is also reported to alter glutamate level and some of its metabolic enzymes. The impact of aluminum exposure on the metabolism of these amino acid neurotransmitters are found to be influenced by dietary protein level (Nayak & Chatterjee, 2002, 2003).

Aluminum ingestion alters behavior and some neurochemicals in rats (Lal et al, 1993). Studies on the effect of Al on the rat brain serotonergic system (Kumar, 2002) concluded that neurochemical changes due to Aluminium were dependent on the duration of exposure and are brain-region-specific. The observed changes may be related to the cholinergic toxicity of Aluminium.

Altered cholinergic metabolism in rat CNS following aluminum exposure has been implicated in reduced learning performance (Julka et al, 1995). Decrease in SOD activity as well as increased oxidative damage to lipids and proteins, altered calcium homeostasis (Julka & Gill, 1996), intraneuronal lipofuscin accumulation (Kaur et al, 2003), necrotic alteration in the CA1, CA2 and CA3 regions of the hippocampus (Sreekumaran et al, 2003) are some aluminum-induced conditions.

Chronic exposure to aluminum has been reported to impair mitochondrial energy metabolism and increase oxidative stress in rat brain leading to oxidative damage (Katyal et al 1997, Nehru and Anand 2005; Kumar et al 2008). A decrease in total glutathione reduced glutathione and oxidized glutathione in cerebrum and cerebellum in developing and developed rats was observed (Anand and Nehru, 2006) following their exposure to aluminum. Morphological changes in mitochondria and nucleus in hippocampus and corpus striatum were also observed in these studies. Phosphorylation induced damage of neurofilaments in cerebral cortex was observed in rats exposed to aluminum (Kaur et al. 2006). Cytoskeleton proteins were found to be aggregated and disrupted in cerebral cortex as revealed by immunocytochemical studies. Neurotoxic effects of aluminum have been linked with modifications in intracellular calcium homeostasis (Kaur and Gill 2005). In an attempt to develop peripheral markers for aluminum toxicity studies were carried out on serum in aluminum treated rats. A decrease in serum cholinesterase and cytochrome oxidase and an increase in glucose – 6 – phosphate dehydrogenase activity were observed in rats chronically exposed to aluminum (Kaur and Gill 2006). Further, overall perturbations in the metabolic profile of serum and urine showed impairment in the tricarboxylic acid cycle, liver and kidney metabolism, along with behavioral changes (Tripathi et al, 2008).

Dua and Gill (2004) reported that exposure to aluminum phosphide affects the redox chain in rat brain and also impairs the electron transfer along the respiratory chain. Exposure of rats to aluminum phosphide also caused an increase in brain lipid peroxidation and a decrease in the activity of antioxidant enzymes (Dua and Gill 2001).

Ethanol may increase pubertal rat's susceptibility to the toxic effects of Aluminium. The combined exposure of ethanol and Aluminium was found to potentiate cholinotoxicity of the two compounds resulting in motor impairment (Rajasekaran, 2000).

Combined treatment of 4,5 dihdroxy benzene 1,3 disulfonic acid di sodium salt (Tiron) and glutathione, attenuated aluminium induced oxidative stress in rat brain (Sharma et al. 2007). Handu and Bhargava (1997) reported that treatment with BR-16A (MentatR, 100 mg/kg/day) for 20 days improved learning and memory in rats treated with aluminium (1000 mg/kg/day) for 40 days.

Bacopa monnieri and Gingko biloba extensively used in Ayurveda, show neuroprotective effects against aluminum toxicity (Das et al, 2002; Jyoti & Sharma, 2006).

Selenium

Treatment with sodium selenite in rats was found to cause behavioral and neurochemical abnormalities (Ahmad et al 2005). Rats were found hyperactive with increase in brain dopamine levels following selenium treatment. Selenium treatment in rats altered cholesterol and phospholipid content in neuroendocrine centres (Islam et al 2004). A significant increase in lipid peroxidation and a decrease in reduced glutathione content were observed in hypothalamus and neuroendocrine centres in these studies. Selenium was also found to alter phospholipids in circadian rhythm centres in rats (Islam et al. 2002).

Tellurium

Treatment with sodium tellurite in mice caused dose dependent effect on brain lipids (Kaur et al 2003 a). Differential effects were observed in cerebrum, cerebellum and brain stem in these studies. An increase in lipid peroxidation and a decrease in the activity of antioxidant enzymes in brain regions were reported in mice treated with sodium tellurite (Kaur et al 2003 b).

Pesticides

Many pesticides classified by the World Health Organisation as highly or extremely toxic are in widespread use, among these organophosphate pesticides (OPs) are a particular public health concern in developing countries, because they are reported to be the cause of majority of acute pesticide poisonings (Cherian et al, 1997; Sudarsanam et al, 2006; Kaur et al, 2007). A number of human cases

have been reported for their neurological disturbances following acute or chronic exposure to pesticides. Besides the fact that such poisonings can be life-threatening, severe poisonings caused by particular OPs have been associated with a persistent neurological impairment that may ensue a few weeks after the recovery from acute poisoning, so-called Organophosphate-induced Delayed Polyneuropathy (OPIDP). Recognized as a clinical entity since 1953, a substantial body of experimental and epidemiological evidence has been published on the subject. Some studies have reported mixed sensory-motor neuropathy , while others have found predominant or exclusive motor neuropathy (Poojara et al, 2003) after severe poisonings with some organophosphate insecticides. The intermediate syndrome (IMS) has been identified as another OP-induced neurotoxic illness that appears after the acute cholinergic crisis but before the expected onset of OPIDP (Singh, 2000; Das, 2000). The pathogenesis of IMS has not been well characterized but is suspected to involve a combination of pre- and post-synaptic dysfunction of neuromuscular transmission as a result of prolonged AChE inhibition. Oxidative stress and antioxidant status in acute OP insecticide poisoning was studied and role of oxidative damage to muscles as a possible mechanism underlying the development of IMS has been identified (Vidyasagar et al, 2004; Dandapani et al, 2003). The organophosphate pesticides exhibit their action by inhibiting AChE enzyme in central and peripheral nervous system. Patients with onset of deep coma 4–7 days after hospital admission showed (Peter et al, 2008) clinical features that had not been previously described.

Neurotoxicity of pesticides may occur due to their ability to cross the blood-brain-barrier (BBB), thereby causing functional impairment. Such damage to BBB has been reported following an exposure to a variety of environmental chemicals and among different species (Sinha & Shukla, 2003). The developing BBB of younger animals is more sensitive to BBB breach as compared to that of adults in experimental animals exposed to pesticides. This is evident from studies with quinalphos, lindane, allethrin and cypermethrin that have shown that rat pups exposed to these pesticides during first few weeks of life show persistent increases in BBB permeability (Gupta et al, 1999; 2000). Further, increased sensitivity of young rats than adults, as reflected in differences in their maximum tolerated doses, neurobehavioural changes, brain and plasma AChE inhibition may help in neurotoxicological risk assessment of triazophos for young animals (Singh & Rishi, 2005). Neonatal quinalphos exposure produces cerebral oxidative stress thus affecting CNS function (Gupta et al, 1998). Exposure to another three pesticides, dichlorvos, lindane, and carbofuran increased BBB permeability in mice also (Sinha & Shukla, 2003). Chronic low-level exposure to dichlorvos causes impaired mitochondrial bioenergetics and apoptosis (Kaur et al, 2007) leading to neuronal degeneration.

Presence of CYP-450 dependent monooxygenase, their isozymes, mRNA expression was demonstrated in neuronal and glial cells and brain microsomes (Dhawan et al 1990, 1992, 1999, Parmar et al 1998; Yadav et al 2006 a, b, Kapoor

et al. 2006 a, b, 2007). Brain CYP450 (CYP) was responsive to transplacental induction by lindane in pregnant rats (Johri et al, 2008 a) and in offspring prenatally exposed to lindane (Johri et al 2007 a, 2008 a, b). As lindane could imprint the expression of cerebral and hepatic CYPs, it may help in identifying the role of these enzymes in developmental neurotoxicity. Effect of deltamethrin and lindane in modulating the activity of these enzymes was also studied and regional specificity in the expression of CYP isozymes reported (Dayal et al. 2001, Parmar et al 2003, Yadav et al. 2006 c, Johri et al. 2006, 2007 b, 2008 a, b).

Chronic dichlorvos exposure in rats caused a decrease both in high and low affinity uptake of choline and cholinergic muscarinic receptors in brain (Raheja and Gill 2007). Activity of adenylate cyclase and cAMP levels in cerebrum, cerebellum and brain stem was also found to be decreased in dichlorvos treated rats suggesting that OP may affect muscarinic receptor linked signaling pathway (Raheja and Gill 2007). Modifications in intracellular calcium homeostasis associated with neuronal dysfunctions was suggested to be a possible mechanism in dichlorvos induced neurotoxicity (Raheja and Gill 2002). Behavioral and functional alterations in dicholorvos treated rats were associated with altered dopaminergic system (Choudhary et al. 2002). Julka et al. (1992) studied effect of dichlorvos on brain antioxidant defense system. A decrease in GSH levels was found to be a potential mechanism in detoxification of dichlorvos in rat brain.

Nimodipine, a calcium channel blocker has been found to attenuate dichlorvos induced neurotoxicity (Choudhary & Gill 2001, Choudhary et al. 2002, 2006).

Synthetic pyrethroids are potent insecticides of high bioefficacy. Behavioural, neuromorphological and chemical effects of deltamethrin have been studied and its neurotoxicity was primarily found to be through modification of sodium gating kinetics; low dose exposure *in utero* also affected the developing brain (Husain et al, 1992 Husain et al, 1994, 1996; Aziz, 2001). Pyrethroid-based mosquito repellants (MR) are commonly used indoors in the form of aerosols, mats, coils, and liquid vaporizers. Rat pups when exposed to pyrethroid-based MR (allethrin 3.6% w/v, 8 h/day through inhalation) during prenatal (GD1-20), postnatal (PND1-30) and perinatal (GD1-PND30) period of development, showed significant oxidative stress in brain regions (Sinha et al, 2006). The hippocampus was the most affected region and further exhibited altered cholinergic functioning. MR inhalation, during early prenatal/postnatal/perinatal life may also have adverse effects on infants leading to central nervous system (CNS) abnormalities (Sinha et al, 2004), if a mechanism operates in humans similar to that in rat pups. Low level exposure to deltamethrin in utero during brain growth spurt period adversely affects the developing brain and the changes persist even up to 12 weeks postnatal period in rats (Aziz et al, 2001).

Postnatal exposure (PND 9-13) of rats to deltamethrin caused a delay in appearance of radial glial fibres that guide the migration of granule cells (Patro and

Patro 2005). A delay in cytogenesis and morphogenesis in cerebellum was also observed later in life following postnatal exposure of rats to deltamethrin (Patro et al. 2007).

Effect of alpha-cypermethrin on brain GABA levels and associated behavior was studied in rats (Manna et al. 2005). Exposure to alpha-cypermethrin at LD50 dose (145 mg/kg) in rats decreased brain GABA levels and was found to potentiate pentobarbitone induced sleeping time and pentylenetetrazole induced convulsion.

Role of phosphoinositide signaling in the neurotoxicity of endosulfan was studied in rats. Exposure to endosulfan (15 mg/kg, once) decreased phosphatidylinositol (PI) and phosphatidylinositol 4,5-bisphosphate (PIP2) without any effect on phosphatidylinositol 4-phosphate (PIP) 4 hours after treatment in rat brain (Subramoniam et al 1994). A marked reduction in brain PI and PIP2 levels was observed in rats treated with endosulfan (15 mg /kg) for 16 days suggesting involvement of phosphoinositide messenger system in endosulfan neurotoxicity.

Clinical studies of toxic gas (methyl isocyanate) poisoning in Bhopal revealed significant cognitive impairment in severely exposed MIC victims (Misra & Kalita,1997).

Solvents & Industrial Chemicals

Organic solvents are widely used in the modern world and seem to be ubiquitous—they are employed in paints, pharmaceuticals, degreasants, adhesives, printing inks, pesticides, cosmetics, and household cleaners. Commonly used solvents include, isopropanol, toluene, xylene, solvent mixtures such as white spirits and the chlorinated solvents, methylene chloride, trichloroethylene, and perchloroethylene.

Most workers suffer from respiratory problems, lung diseases and skin infections through constant exposure to glue and fumes. They are also exposed to risk of nasal cancer, neurotoxicity and adverse physical factors. Organic solvents present in adhesives and glues have been shown to cause shoemaker's paralysis (Tiwari, 2005) that manifests as a more or less severe form of paralysis. Pathophysiology of n-hexane neuropathy was reflected in screen printers (Puri et al, 2007). A study provides electrophysiological evidence that rubber factory environments affect the conduction processes in optical pathways (Tandon & Kumar, 1997) and therefore can objectively evaluate the toxic effects of chemicals on the central nervous system.

Methanol, widely used as a solvent, antifreeze and, in particular, as a solvent for shellac in varnishes, an important alternative motor fuel in many countries, and used as an adulterant in illicit country liquor. Many epidemics of human intoxication of methanol have been described worldwide (Liu & Daya, 1996; Laranjeria & Dunn, 1998; Aziz et al, 2002). Neurobehavioral studies have revealed impaired motor and

cognitive functions which were interestingly ameliorated by ethanol (Sandhir & Kaur, 2006). The developing brain is vulnerable to methanol toxicity which could be attributed to poor development of the blood–brain barrier, as well as lack of an efficient drug-metabolizing enzyme system. A possible role of folic acid has been suggested in methanol-induced neurotoxicity (Aziz et al. 2002) as methanol exposure during growth spurt period adversely affects the developing brain, the effect being more pronounced in folic acid deficient rats as compared to folic acid sufficient rats.

Ethanol (EtOH) also is a solvent, and there are numerous reports on neurodevelopmental effects of alcohol. It outweighs by far any evidence for effects of other solvents. Chronic EtOH ingestion is directly associated with serious neurological and mental disorders. The presence of nutritional deficiencies contribute to neuropsychiatric syndromes such as Wernicke's encephalopathy, Korsakoff's syndrome and polyneuritis.Hyperleptinaemia-induced oxidative stress and enhanced ATPase activities may be important pathogenic factors in brain toxicity (Balasubramanian & Nalini, 2006).

Occupational exposure to gasoline has been linked to neurotoxicity. Different behavioral parameters of workers exposed to xylene and toluene in a major heavy electrical industry were studied (Gupta et al, 1990). Immediate and delayed memory, visual ability, visual learning and psychomotor ability were compared with those from unexposed subjects. Immediate and delayed memory was affected among both directly and indirectly exposed workers.

Polychlorinated biphenyls (PCBs) are a class of widely dispersed and environmentally persistent organic compounds. PCBs exhibit a wide range of toxicological effects including neurotoxicity and oxidative stress in rat brain regions by decreasing the activities of antioxidant enzymes, which can be protected by Vitamins C and E (Venkataraman et al, 2007; Sridevi et al. 2007).

Alteration in the sensitivity of striatal dopamine receptors leads to neurochemical and behavioural dysfunction.(Khanna et al,1991; 1994).Ravindranath and Pai (1991) have used rat brain slices as an in vitro model for acrylamide and 1-methyl-4-1,2,3,6-tetrahydropyridine (MPTP) neurotoxicity studies. The neurotoxicity of acrylamide has been extensively studied with respect to mammalian species and the overt signs of neurotoxicity are consistent across species. For the detoxification of xenobiotics, brain GSH may be playing an important role in situ within the central nervous system as exhibited by acrylamide (Bangalore et al, 1992; Shivakumar & Ravindranath, 1993) and lead (Jindal & Gill, 1999) exposure.

Natural and other Neurotoxicants

Cannabis was found to affect .the blood brain barrier permeability and cholinergic – muscarinic receptors in mice. (Agarwal et al. 1989).

Lathyrism, one of the oldest neurotoxic disease known to man, results from excessive consumption of the chickling pea Lathyrus sativus which contains beta-N-Oxalyl amino-L-alanine (L-BOAA), a naturally occurring non-protein amino acid. One of the primary effects of L-BOAA toxicity is the inhibition of mitochondrial complex I selectively in the motor cortex and lumbar spinal cord (Ravindranath, 2002). Thiol oxidation and concomitant mitochondrial dysfunction have been considered to be primary events leading to neurodegeneration (Sriram et al. 1998).

L-BOAA also causes oxidative stress by inhibiting cystathionine gamma-lyase present in neuronal cells (Diwakar and Ravindranath, 2007). This subsequently could be playing an important role in maintaining glutathione and protein thiol homeostasis (Kenchappa et al. 2002; Kenchappa and Ravindranath, 2003) in brain thus protecting CNS.

Herbal and Unani extracts / preparations have been tested to investigate their neuroprotective efficacy in rat model of Parkinson's disease induced by 6-OHDA (Ahmad et al 2005 a,b,c, Ahmad et al 2006 a, b). Adenosine and selenium were found to slow down the progression of neurodegeneration in 6-OHDA induced Parkinsonism in rat model (Zafar et al. 2003 a, b). Streptozotacin induced cognitive impairment were found to be prevented by Coenzyme Q10, a lipophilic anti-oxidant (Ishrat et al. 2006) and Khamira Abresham Hakim Arshad Wala (KAHAW), an extensively used preparation in Indian system of Unani medicine (Khan et al. 2006).

Exposure to adriamycin was found to enhance oxidative stress in brain and that decreased following in vitro addition of GSH or vitamin E to brain homogenates (Julka et al. 1993). Flunarizine, a calcium channel antagonist and vasodilator was found to be neuroprotective as it enhanced functional recovery following sciatic nerve crush lesion in rats (Patro et al. 1999).

Transient neurotoxicity of 5-fluorauracil (5-FU) has been reported in a case study (Selvamani et al. 2007). Although neurotoxicity of 5-fluorouracil is rare, it was suggested that clinicians should be aware and careful of its adverse acute neurological effects. A patient of acute myeloid leukaemia was found to exhibit cerebellar toxicity and peripheral neuropathy while given high dose cytarabine arabinoside (HIDAC). Treatment with methyl prednisolone improved the symptoms and suggested role of immune mediated mechanism in neurotoxicity of cytarabine (Malhotra et al. 2004). Long term use of metronidazole has been reported to cause motor sensory neurotoxicity involving lower limbs (Kapoor et al. 1999).

Conclusions

Neurotoxicology is an important discipline of neurosciences in Inidia and significant amount of research both clinical and experimental is being carried out in some institutions in the country. In view of the large scale use of metals, pesticides and other neurotoxic chemicals and agents and their association with

neurological disorders like Parkinsons disease, Alzheimer and other cognitive disorders more focused research is needed. Awareness of such associations, alterd response of individuals due to differences in age and nutritional status among the clinicians is extremely important. The recent reports of susceptibility to chemicals due to genetic make up makes this all the more significant. New precautionary approaches with emphasis on the unique vulnerability of the developing brain, particularly, at long-term low-level exposure to neurotoxic agents are needed both at experimental and clinical levels.

The process of disease development whether due to an organic cause or induced by an chemical is quite similar and therefore identification of impact of chemical exposure at early stages, prediction of the outcome of exposure and identification of the population sensitive to chemicals or diseases are challenging tasks but key to prevention of health ailments. Hence, identification of biomarkers, which could help in identification of neurotoxicological diseases and persons susceptible to them much before an irreversible damage is done, would be of unestimatable value. There are few successful examples of collaborations between basic and clinical neuroscientists in some of the above area; a greater collaborative effort is needed. There is also need of structured training and setting up centres of excellence in neurotoxicolgy.to provides better understanding of the mechanisms and management of such disorders.

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