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Review of the multiple chemical exposure factors which may disturb human behavioral development

Summary

Previous research both in humans and laboratory animals provides evidence that prenatal exposure to metals, pollutants and drugs may impair the neurobehavioral development of the offspring. This may induce mental and psychomotor disturbances as well as learning, behavioral and sensory disorders. However, proof for a strict causality between some low-level exposures to chemicals and behavioral developmental dysfunctions, is often considered still not to be established. The pertinent studies on neurobehavioral developmental toxicity of individual substances (lead, cadmium, organic solvents, PCBs, alcohol, nicotine, diazepam) are reviewed, and the methodologies and conclusions, the missing aspects and the existing problems which still need to be solved in further studies, are discussed. In addition, the necessity of undertaking a broad prospective cohort study on multifactorial influences on the behavioral development of children is emphasized.

Humans are exposed to a multitude of factors which influence their psychological development in a multidimensional living space. Among these factors, a large variety of chemicals, including low-level environmental heavy metals (lead, cadmium), organic solvents, PCBs, drugs of abuse (alcohol, nicotine) and medical drugs (diazepam) may disturb the development of the central and peripheral nervous systems. In addition, because behaviour is a functional indicator of the net sensory, motor, and integrative processes occurring in the central and peripheral nervous system[1], the special behavioural characteristics of infants and young children are important in the context of exposure to chemicals. For many chemicals, the existing toxicological, and especially neurobehavioral, developmental data are inadequate for safety evaluation. A lot of nervous system-related health effects occur at lower exposure concentrations than do other effects for certain chemicals[2]. To be exposed to such agents or a combination of them in prenatal life may cause deficits of the behavioral development of children in specific periods. Effects may include impaired mental and psychomotor development, learning, behavioral and sensory disorders. The intention of this review of pertinent studies on behavioral teratology is to present the results of behavioral studies of the effects of individual environmental pollutants, drugs and other special agents on both humans and animals and to discuss the conclusions of the studies, the missing aspects, and the problems which need to be solved by further investigation.

Lead

The effects of lead on neurobehavioral development have been extensively investigated in humans, especially children. In much behavioral research, children's cognitive functions have attracted the most attention. Assessments of cross-sectional epidemiological studies of lead and IQ in Children have led to the conclusion that lead exposure at blood lead levels below

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Species	Effect	Range of ages when measured	Lowest blood lead level, µg/dl
Human	2–8 pt.MDI* deficits	3 months – 2 years	10–15 perinatal
	4–7 pt.GCI* deficits	4–5 years	≥10 at 2 years
Primate	Impaired reversal learning (concept-formation)	1.5 months – 9 years	<15 steady state
	Perseveration	1–8 years	<15 steady state
	Response variability	2 months – 8 years	<15 steady state
Rodent	Increased operant response rate	50 days	10–20 at 100 days
	Perseveration	4–7 weeks	<20 at 8 weeks
	Response variability	7–20 weeks	15–20 at 100 days

* Abbreviations: MDI = Bayley Mental Development Index; GCI = McCarthy General Cognitive Index

Table 1. *Comparison of developmental neurobehavioral lead LOAELs in humans, primates, and rodents*[15].

30 µg/dl can result in a reduction in the children's IQ scores [3,4].
Prospective epidemiological studies have found that there exists a link between deficits of 2–8 points on the Mental Development Index (MDI) of the Bayley Scales of Infant Development (BSID) and blood lead levels of 10–15 µg/dl and possibly lower [5,6,7]. The reductions in scores on the McCarthy Scales of Children's Abilities at age 4–5 years are significantly associated with early postnatal lead exposure [8,9].
Other behavioral end-point studies such as impairment of language and speech at age 2–3 years have shown relations to prenatal lead exposure [10]. Children's attention deficit disorder with hyperactivity has also been found associated with lead exposure. However, it is not clear how lead affects children's general activity levels [6,11–14].
Many animal studies have been conducted to evaluate rather complex neurobehavioral performances in rodents and nonhuman primates exposed to relatively low levels of lead. Davies et al.[15] summarized some of the more reliably established lowest observed adverse effect levels (LOAELs) for lead developmental neurotoxicity in humans and animals (Table 1).
The adverse effects of lead on the behavioral development of children have been proved by many studies. The remaining problems are to understand how lead affects some categories of behavior (e.g. general activity levels) in children, and to find the most sensitive or valid methods or instruments for assessing the effects of lead on behavioral endpoints (e.g. social and emotional adjustment; cognitive functions).

Cadmium

Cadmium, because of its exceptional ability to accumulate continuously in the body throughout life, and because of its high toxicity, also represents an increasing hazard for the general population.
Only a few studies have been directed at the effects of Cd on the developing organism. But one may suspect that Cd will be highly toxic during the early stages of development, and the sensitivity of the young to early Cd exposure should be considered, because organisms are particularly vulnerable during periods of rapid growth [16], and in the newborn absorption of metals from the gut is much higher than in adults [17]. Research on a human population of mothers who smoke excessively has shown that they quite often deliver small-for-date babies. This may be attributed to the high amount of Cd in tobacco smoke [18]. A common characteristic associated with early Cd exposure has been a reduction in the birth weight of the children [19]. Further, Murthy et al.[20], observed in regard to maternal exposure in rats that females retain about two times as much of an oral dose of Cd as do males. Thus, not only is the newborn more susceptible to the toxic effects of Cd, but pregnant females have the capacity to accumulate greater body burdens than males.
Animal studies have shown that perinatal exposure to low levels of Cd can result in some behavioral alterations (e.g. in activity and cognitive ability) of exposed offspring [21,22]. But the mechanism by which these changes occur is less clear. Another problem in considering the effect of Cd is its influence on the status of essential trace metals. It has been well documented that exposure to Cd can alter

both the absorption and the metabolism of zinc, copper, iron and other metals[23]. Changes in these essential metals in the developing organism can cause dysfunction in many organ systems, including the CNS[24]. Thus, it should be further determined whether the Cd toxicity is of a direct or an indirect nature.

Organic Solvents

Organic solvents are derived from many different chemicals and are present in products such as paints, glues, adhesives, coatings, degreasing agents, polymers, dyes, plastics, textiles, printing inks, agricultural products, and pharmaceuticals[25]. Because of the widespread use of these compounds in industrial products and processes, a larger population is exposed to solvents than to any other type of environmental chemical.

However, for many industrially and commercially used organic solvents, little or no information regarding their potential effects on the nervous system is available[26]. The majority of cross-sectional studies on occupationally exposed workers demonstrated an excess of neuropsychiatric symptoms and usually lower performances in psychological tests in solvent-exposed workers compared with nonexposed workers[27]. A recent cross-sectional occupational study in Switzerland concerning the toxicity of hydrocarbons showed an increased prevalence of smell and/or taste disturbances in the heavily exposed group[28]. All longitudinal studies have shown that there is an increase in awards of early disability pensions due to neuropsychiatric disorders among such workers[27].

10 of 12 solvents which were tested gave rise to deficits in various factors linked with behavioral development (such as growth, activity, neurotransmitters, learning and memory, reflex and motor characteristics) in experimental animals. A series of acute and chronic solvent effects on the central or peripheral nervous system have been observed[25,29]. Thus, the potential of organic solvents to produce persistent changes in brain functions has become an issue of considerable importance. Pre-, peri- and postnatal exposure to organic solvents and the adverse effects on children should be considered and studied.

Polychlorinated Biphenyls (PCBs)

PCBs have caused significant environmental contamination because of their widespread use in industry, leading to high levels of these compounds in the food chain of animals and humans. The disposition of PCBs in various human tissues and body fluids (milk, maternal blood, fetal blood, semen, and fat) has been investigated, and increased accumulation has been observed after long-term exposure[30]. PCBs were detected at an average level of 109 µg/kg in whole human milk in Switzeland in 1974, and at 33.7 µg/kg (range 10–85) in Zürich in 1983[31].

In humans, PCBs are toxic, and are known to cross the placenta and to be teratogenic in human infants exposed at high levels. Two major incidents of PCB poisoning have occurred in Asia; women pregnant during or after exposure had children who were developmentally impaired[32,33]. In two U.S. studies, children were found to have hypotonia and hyporeflexia at birth after prenatal exposure, delay in psychomotor development according to the Bayley Psychomotor Index at 6 and 12 months, and poor visual recognition memory at 7 months[34]. In Jacobson's study[35], prenatal exposure (assessed by cord serum PCB levels) was associated with lower weight. Reduced activity was associated with both contemporary body burden (assessed by 4-year serum PCB level) and exposure to PCB contaminated breast milk. The effect of maternal milk on activity was strongest in children of women with higher than average PCB levels who breast fed for at least 12 months.

Alcohol

It is known that the fetal alcohol syndrome (FAS), which includes distinct craniofacial anomalies, growth retardation and mental retardation, is due to chronic maternal alcohol consumption[36]. The incidence of FAS is about 1 or 2 cases per 1,000 live births, and about 8,500 infants (6,000–11,000) are born each year in the United States with either a major or a minor anomaly related to prenatal alcohol exposure[37].

A great deal of research on the effects of alcohol during gestation has been done, including case, epidemiologic, and animal studies.

Case studies have provided a clinical profile of FAS, as mentioned above, and indicated the dose-effect relationship. FAS is associated only with high chronic maternal alcohol consumption, whereas exposure to lower levels of alcohol during gestation may result in developmental and neurobehavioral dysfunctions[38,39].

Epidemiologic studies on prenatal exposure to alcohol have demonstrated the magnitude of the long-term consequences of neurobehavioral effects, such as deficits in the ability to sustain attention problems in behavior, persistent physical deficits, and reductions in specific academic skills, in groups of children who were exposed to alcohol at levels which do not necessarily result in clinically significant morphological effects. In these studies, some confounding factors which can also influence development, such as smoking, nutrition, and the use of other drugs, were

separated from the effects of alcohol exposure in the statistical analysis [40–45].

In animal studies, a variety of neurobehavioral effects which are qualitatively similar to those described in children with a history of gestational alcohol exposure, have been detected following prenatal alcohol exposure [46,47]. Some recent studies have shown that prenatal ethanol exposure alters the sensitivity of the postsynaptic dopamine systems which are important to locomotor activity, in young male rats [48]. The neonatal alcohol exposure can produce deficits in response inhibition (passive avoidance performance) [49].

Driscoll and her coleagues have compared the behavioral effects of prenatal alcohol exposure in humans and in animal models. They evaluated characteristics such as hyperactivity, attention deficits, mental retardation, poor coordination, and developmental delay [50]. The studies demonstrated that the magnitude of the observed effects was generally dose-related for both humans and animals.

In summary, alcohol is a potent teratogen, associated with FAS, with growth retardation and with behavioral alterations in neonates prenatally exposed to various dosages. Questions remain about the long-term consequences of prenatal alcohol exposure. Because of the potential interaction between development and the postnatal rearing environment, further investigation should examine such influences upon the interpretation of results. The effects of alcohol in combination with other toxins should also be examined.

Nicotine

The numbers of women smoking during the prenatal and perinatal period are estimated to be 30.9% and 25.5% respectively [51], and it is generally observed that tobacco smoking during pregnancy leads to intrauterine growth retardation and smaller infants than those of non-smoking mothers [52]. Follow-up studies have shown that children whose mothers smoked during pregnancy more frequently exhibit hyperactivity, a short attention span, and lower scores on spelling and reading tests. These behavioral abnormalities have been associated with elevated neonatal hemoglobin levels and low birth weights [53]. At 14 years of age, offspring of mothers who smoked were not up to normal standards in reading, mathematics and general ability, even when social and biological factors were taken into account [54], which demonstrated that they had long-term learning deficits.

Werle's review [55] mentioned that epidemiological data indicate that smoking during pregnancy increases the risk of spontaneous abortion. *Abruptio placentae* and *placenta praevia* have been found to be the cause of perinatal mortality in a greater proportion of the offspring of smokers than those of non-smokers. In a retrospective study, the parents of 306 mentally retarded children (cases) and 322 physically handicapped children (controls) were investigated concerning their life-style and habits from 3 months before conception to 6 months post-partum. This study suggested that paternal smoking of pipe or cigars and maternal alcohol consumption just before, during, and after pregnancy are related to a higher incidence of mental retardation in offspring. No such association was seen for cigarette smoking, and no effects were found for paternal alcohol consumption. Maternal smoking was related to low birth weight and prematurity [56]. Other studies have suggested a similar negative relationship between maternal nicotine use during pregnancy and infant mental development [57,58].

Animal studies have also provided evidence to support the suggestion that nicotine may cause developmental neurotoxicity. Sonawane [59] reported a significant weight reduction at birth, and later abnormalities of reproductive anatomy and functions in both males and females. Recent studies show that prenatal nicotine increases the susceptibility to electroconvulsive shock (ECS) in adult rats, and demonstrate long-lasting deleterious effects induced by nicotine exposure during fetal life [60]. In addition, an in vitro study confirmed previous reports that in utero, nicotine leads to growth retardation and retards development of the nervous system. Particularly the forebrain, as well as the branchial arches were impaired [61].

Diazepam (DZP)

DZP, the most frequently used benzodiazepine (BZD), has been utilized extensively since 1960 to modify behavior in a wide variety of clinical conditions, particularly in obstetric care [62]. It has been reported [63] that exposure to DZP during the prenatal period results in the "floppy infant syndrome" in newborn babies who have significant plasma levels of diazepam and of its active metabolites. In a prospective study, a benzodiazepine embryofetopathy has been detected in more than 5000 live births where the mothers had high benzodiazepine serum concentrations at the time of the birth [64]. In the higher dose group, there are a series of dysmorphic signs. At lower benzodiazepine doses the syndrome includes hypotonia with hyperexcitability, delayed motor and mental development and perceptual disorders, and hyperactivity and learning disabilities at a later age. In Zielhuis's study [65], it was found that behavioral problems in both boys and girls were associated with the use of psychopharmaceuticals during pregnancy.

In animal studies, DZP has been shown to depress a variety of behaviors in rats and mice. These include defensive burying behavior in rats, saccharin-induced drinking, a fear-enhanced startle response, and a biphasic effect on locomotor and exploratory behavior[66]. In addition, less rearing and longer latencies in an open field were observed, and large and significant differences appeared both in running time and error measures between DZP and control animals[67]. Prenatal exposure to DZP and BDZ have been shown to produce transient depression of olfactory guided behavior (nest odor behavior) in suckling offspring, and increased sensitivity to an opiate (morphine)[68], a faster recovery from the initial depression after 1 mg/kg of muscimol at 14 days and a lack of rebound hyperactivity at 21 and 28 days of ages[69].

The nature of the physiological or molecular mechanisms responsible for the floppy infant syndrome are little known, and even less is known about mechanisms that mediate the long range behavioral consequences of prenatal exposure[67]. One can also question whether the effects of diazepam exposure combined with exposure to other chemicals or drugs are synergistic or antagonistic. Further research is needed to explore the effects of prenatal exposure on these neurotransmitter systems, which play an important part in mediating arousal, activity level, attention and memory processes, to evaluate the potency of drug mixtures used.

Conclusion

Research has offered much evidende that there are harmful effects of environmental metals and other pollutants and drugs on children, especially after prenatal exposure. However, in spite of many data pointing in this direction, a strict causality between some low-level exposures to chemicals and behavioral developmental dysfunctions is still considered not to be proven. Doubts about such conclusions have arisen in view of the importance of confounding factors, which may not have been considered in many of the studies mentioned. In fact, man is exposed to many varieties of natural and artificial substances simultaneously, so it is hard to say whether the harmful effects on humans are caused by only one single chemical. In addition, psychological phenomena may be caused by many other factors (education, environment, genetical factors etc.) which may themselves be correated with exposure to chemicals, so that the demonstrated links with developmental toxicity may be only indirect.

Only a few human studies have been done which investigate effects of prenatal exposure to several agents, e.g. to medical drugs (Diazepam, Benzodiazepines[64]), to drugs of abuse (alcohol, nicotine[53,43]), or to environmental pollutants (PCBs[34]). So far, no study has considered all the possible causative factors, including interactions, between several substances, which may be at the origin of developmental deficiencies in the behaviour of children. Furthermore, no epidemiological study on effects on behavior has ever been done in Switzerland. A multifactorial prospective study in German-speaking Switzerland, considering as many social and toxicological determinants of human behavioral and functional development as possible, would therefore, be an important undertaking.

Soz Präventivmed 1995; 40: 209–217

Zusammenfassung

Übersicht über die mehrfachen chemischen Expositions-Faktoren, welche die menschliche Verhaltensentwicklung stören können

Frühere Untersuchungen sowohl am Menschen als auch am Labortier zeigten, dass vorgeburtliche Exposition auf Metalle, Umweltstoffe, Drogen und Medikamente die Entwicklung des Nervensystemes und des Verhaltens von Kindern stören können. Dies kann Störungen der geistigen und psychomotorischen Entwicklung sowie Lern-, Verhaltens- und Wahrnehmungstörungen bewirken. Trotzdem wird oft angenommen, dass ein Beweis für eine strikte Kausalität zwischen gewissen geringfügigen Expositionen auf Chemikalien und Dysfunktionen der Verhaltensentwicklung noch nicht erbracht worden sei. Die relevanten Studien über die Toxizität individueller Substanzen (Blei, Cadmium, organische Lösungsmittel, PCBs, Alkohol, Nikotin, Diazepam) auf die Entwicklung des Nervensystemes und das Verhalten sind zusammengefasst, und die Methoden, Schlussfolgerungen, die fehlenden Aspekte und bestehenden Probleme, welche durch weitere Studien gelöst werden sollten, werden besprochen. Zudem wird die Notwendigkeit hervorgehoben, dass eine breite prospektive Kohortenstudie über die multifaktoriellen Einflüsse auf die Verhaltensentwicklung von Kindern durchgeführt werden sollte.

Résumé

Revue sur les multiples facteurs d'exposition chimique pouvant perturber le développement comportemental humain

Des travaux de recherche sur les humains et sur des animaux de laboratoire ont livré de l'évidence que l'exposition prénatale à des métaux, des poluants, des droges et des médicaments peut déranger le développement du système nerveux et du comportement des enfants. Ceci peut inclure des perturbations du développement mental et psychomoteur, ainsi que des dérangements de l'apprentissage, du comportement et de la perception. Toutefois, il est souvent admis que la preuve n'a toujours pas été établie qu'il existe une causalité stricte entre l'exposition à bas niveau à certains produits chimiques et des dérangements du développement comportemental. Des études importantes sur la toxicité de certaines substances (plomb, cadmium, dissolvants organiques, PCBs, alcohol, nicotine, diazepam) sur le développement du système nerveux et du comportement sont présentés et les méthodologies, les conclusions, les aspects manquants et les problèmes existants qui doivent être résolus par des études futures, sont discutés. En plus, on insiste sur la nécessité d'entreprendre une large étude prospective cohorte sur les influences multifactorielles sur le développement comportemental des enfants.

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