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Diet–brain connections: role of neurotoxicants

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Abstract

In certain cases, the consumption of food or beverages can lead to intoxication and disease. Such food-induced intoxications may be due to microbial toxins, to toxic substances naturally occurring in some foods, or to contaminants or residues of various kinds. Some of these agents have neurotoxic properties and may contribute to the etiology of certain psychiatric disorders or neurodegenerative diseases. This paper reviews a selected number of dietary neurotoxicants that naturally, or as a result of human interventions, find their way into food or beverages, and have been associated with neurotoxic outcomes in humans. Chosen examples include domoic acid, a phycotoxin associated with amnesic shellfish poisoning; β-*N*-oxalylamine-L-alanine (L-BOAA), present in chickling peas and believed to be responsible for neurolathyrism; and two alcohols, methanol and ethanol, which can cause severe neurotoxic effects in adults and the developing fetus.

Keywords: Neurotoxicants; Domoic acid; β-*N*-oxalylamine-L-alanine; Methanol; Ethanol

1. Introduction

While it has been long suggested that brain functions can be affected by what one eats or drinks, only recently have specific effects of diet and the brain been established, and their molecular and cellular basis explored (Mattson, 2002). Normal components of the diet (e.g. folic acid, choline, fatty acids) are known to profoundly affect the developing and adult nervous systems, and evidence has also accumulated indicating that consumption of certain food and beverages may negatively affect the nervous system because of the presence of specific neurotoxic agents such as microbial toxins, toxic substances occurring naturally in some foods or present as contaminants, or residues of various kinds.

Some of the most dangerous cases of acute poisoning are caused by neurotoxins (Botulinum toxins), derived from *Clostidrium botulinum*, which inhibit the release of acetylcholine leading to paralysis, and can be lethal at doses as low as 10 μg (Grunow, 1999). Several neurotoxic agents present naturally in food (e.g. isoquinolines), or produced in some cases by algae (e.g. domoic acid) and found in shellfish or seafood, have been associated with neurodegenerative diseases or severe episodes of neurotoxicity. Another example of severe neurotoxicity linked to food is that of bovine spongiform encephalopathy (mad cow disease) which has been associated with consumption of beef from improperly fed cattle, and that can have devastating effects on humans (Dormont, 2002). Of recent concerns is also the formation of a known neurotoxic compound, acrylamide, in certain food as a result of some type of cooking (Sharp, 2003).

Food contaminants may include pesticide residues, heavy metals or persistent pollutants such as polychlorinated biphenyls (PCBs). Residues of certain pesticides in food have been suggested to be of concern for possible developmental neurotoxicity (Goldman and Koduru, 2000) or to represent a risk factor for neurodegenerative diseases such as Parkinsons's disease (Lockwood, 2000). Methylmercury is present in most seafood and has been associated with large episodes of neurotoxicity in the past (e.g. Minimata Bay), and more recently with subtle developmental neurotoxic effect in populations heavily relying on fish for their diet (Steuerwald et al., 2000). PCBs can also be found in seafood and other foods and have also been associated with developmental neurotoxicity. These compounds, like other pollutants such as polybrominated diphenyl ethers (PBDE) can also be found in maternal

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milk, which poses additional concern for developmental exposure (Branchi et al., 2003; Winneke et al., 2002).

This brief review will focus on a selected number of neurotoxicants present in the diet. These include domoic acid, a phycotoxin associated with amnesic shellfish poisoning; β-*N*-oxalylamine-L-alanine, an excitatory neurotoxin present in chickling peas, thought to be responsible for neurolathyrism; methanol, found in adulterated beverages, which can cause severe damage to the visual system; and ethanol, found in alcoholic beverages, which is one of the most abused legal substances, and can have deleterious effects on the developing brain. These compounds were chosen to represent examples of different types of neurotoxicants present in food or beverages and to highlight different aspects of the general issue of the contribution of diet to neurotoxic disorders in humans.

2. Domoic acid

In November 1987, a total of 250 reports of illness were received in Eastern Canada related to the consumption of mussels. Symptoms were primarily of gastrointestinal nature, but included severe headache and loss of memory, particularly short-term (Perl et al., 1990). More than 20 individuals required hospitalization, with confusion, disorientation and inability to recall the recent past as prominent features of their clinical presentation (Perl et al., 1990). Seizures, myoclonus and abnormality of arousal ranging from agitation to coma were also present; four individuals died within 4 months of ingesting mussels. Neuropathological studies carried out in the latter revealed neuronal necrosis or loss, and astrocytosis, predominantly in the amygdala and the hippocampus (Teitelbaum et al., 1990). Several months after poisoning, 12 patients had severe anterograde memory deficits and clinical and electromyographic evidence of motor or motor-sensory neuropathy (Teitelbaum et al., 1990). The causative agent of this mass intoxication was soon identified as domoic acid (DA), a neuroexcitatory toxin whose source was traced to a bloom of the diatom *Pseudo nitzschia* (Mos, 2001). Since this outbreak, more cases of intoxication linked to the presence of DA have been reported; humans only suffered mild poisonings, while several hundred animals were killed by DA-contaminated foods (Mos, 2001).

A large number of experimental studies carried out in rodents and non-human primates have delineated the features of DA-induced neurotoxic damage, whose pattern is rather similar in all species. Clinical signs include sluggishness, stereotypic scratching (rodents and primates), gagging/vomiting (primates), profuse salivation, “wet dog” shakes (rodents), tremor and seizures (Scallet et al., 1993; Sobotka et al., 1996; Tryphonas et al., 1990a, 1990b). Memory impairment, particularly working memory deficits, is a primary feature observed in DA-treated rats or mice (Sutherland et al., 1990; Clayton et al., 1999). As previously seen in humans, Cynomolgus monkeys exposed to DA showed damage to the hippocampus, particularly the CA2 regions, and other subfields (CA1, CA4) at higher doses (Scallet et al., 1993). Lesions consisted in vacuolation of the neuropil, astrocytic swelling and neuronal shrinkage, and were also detected in the area postrema, the hypothalamus and the inner layers of the retina (Tryphonas et al., 1990a). Similar lesions were also found in rodents (Tryphonas et al., 1990b; Sutherland et al., 1990; Sobotka et al., 1996).

It was apparent early on that the pattern of brain damage observed in humans and subsequently in animals, following exposure to DA, resembled that seen following administration of kainic acid (KA; Teitelbaum et al., 1990). DA is indeed structurally related to KA, an excitatory amino acid that exert its neurotoxicity by activating specific subtypes of receptors for the neurotransmitter glutamate. Earlier studies had shown that DA has a higher affinity for KA receptors than KA itself (Zaczek and Coyle, 1982). A comparison of the DA and KA effects in vitro and in vivo confirmed that DA acts via KA receptors, and is 3–20-fold more potent (depending on the measured end-point) than KA itself (Stewart et al., 1990; Hampson and Manalo, 1992). KA receptors are selectively distributed in the nervous system; they have been identified in the spinal cord, in the dorsal root ganglion neurons and in trigeminal neurons, in the hippocampus, the cerebellum and the amygdala (Bleakman, 1999). The distribution of KA receptors coincides for the most part with the pattern of damage seen after administration of KA or DA.

There is convincing evidence that glutamate precipitates oxidative stress in brain cells, primarily through activation of ionotropic receptors (Coyle and Puttfracken, 1993). With regard to KA receptors, increasing evidence derived from in vitro and in vivo studies supports a role for free radicals in neurotoxicity. For example, in rat cortex, both KA and DA were found to increase levels of reactive oxigen species (Bondy and Lee, 1993). In rat cerebellar granule cells, KA was shown to increase lipid peroxidation, and this effect, as well as KA-induced cytotoxicity, was antagonized by antioxidants (Puttfarcken et al., 1993). Similarly, in vivo administration of KA increased free radical formation and lipid peroxidation in brain (Sun et al., 1992; Gupta et al., 2002). Increased oxidative stress and neuronal degeneration induced by KA were antagonized by antioxidants and free radical scavengers (Miyamoto and Coyle, 1990; Gupta et al., 2002).

Age is believed to be an important factor modulating the neurotoxicity of DA. In the Eastern Canada outbreak, the four mortalities were elderly subjects, all over 70 years in age, and overall, the older adults were more likely to suffer memory loss (Perl et al., 1990). Such increased sensitivity to DA neurotoxicity in aging may be due to a decreased clearance of DA by the kidneys (Truelove and Iverson, 1994), or by decreased antioxidant defenses in the brain of aged individuals (Kerr et al., 2002). Similarly, neonates and young children may be at higher risk for DA neurotoxicity, because of incomplete blood–brain barrier, low serum clearance and low antioxidant defense mechanisms (Xi et al., 1997). Studies in rodents have indeed shown that pups were more sensitive than

adults to the neurotoxicity of shellfish extracts containing DA (Bose et al., 1989).

In summary, it is evident that consumption of DA contaminated foods produces lasting and serious effects in its victims. In humans, high doses can lead to death, while lower doses have caused permanent loss of short-term memory. The neurotoxic effects of DA have been traced to its binding to a subset of receptors for the excitatory neurotransmitter glutamate, namely the KA receptors. Overstimulation of KA receptors by DA leads to increased oxidative stress eventually resulting in neuronal cell death. To prevent episodes of shellfish poisoning like the one in Canada, rigorous monitoring of DA levels have been implemented, as *P. nitzschia* blooms cannot currently be well predicted (Mos, 2001). For razor clams, a regulatory action level of 20 mg/kg tissue has been set (Marien, 1996) based on available toxicological data and estimates of US shellfish consumption. However, in certain populations (e.g. native American tribes in the US Pacific Northwest) shellfish consumption can be higher. DA levels of 5–20 mg/kg tissue are often found in razor clams or blue mussels and levels of DA as high as 300 mg/kg tissue were seen in razor clams (Adams et al., 2000). It was estimated that mussels involved in the Canadian outbreak contained extremely high levels of DA, ranging from 300 mg/kg issue to up to 1 g/kg (Perl et al., 1990).

3. β-*N*-oxalylamine-L-alanine (L-BOAA)

Consumption of the leguminous plant *Lathyrus sativus* (chickling pea or grass pea) still occur in parts of the world, such as India, Bangladesh or Ethiopia, particularly during periods of flood or drought (Hugon et al., 2000). Heavy ingestion of *L. sativus* is associated with the motor neuron disease lathyrism (neurolathyrism). The clinical features of this disease resemble those of hereditary spastic paraplegia, and are characterized by muscle spasms and weakness in the legs, progressing to spastic paraparesis, which, in the most severe cases, leads to a crawling stage where individuals are unable to move their legs (Hugon et al., 2000). The best documented evidence of a causal relationship between heavy consumption of grass peas and development of spastic paraparesis comes from the description of a group of prisoners during World War II who were fed grass peas as their main food (Kessler, 1947). Most developed lathyrism, and a follow-up study indicated the persistence of spastic paraparesis dominated by marked stiffness, mild weakness and cramps in the legs (Cohn and Streifler, 1981). Clinical signs of lathyrism are also seen in several animals species following ingesting of *L. sativus*, with horses being exceptionally vulnerable to its neurotoxic effects (Hugon et al., 2000).

The neurotoxicity of *L. sativus* is believed to be due to the aminoacid β-*N*-oxalylamine-L-alanine, which is found in this and other plants (Spencer et al., 1986). Animal studies have shown that administration of L-BOAA causes hindlimb weakness and paralysis and central nervous system damage. In non-human primates, early reversible sign of spastic paraperesis occur, followed by evidence of central motor disorders after 3–10 months (Spencer, 1999). However, doses 10–100-fold higher than those effective in humans are required. This is thought to be due to differences in L-BOAA toxicodynamics and metabolism between humans and macaques and/or to the presence of a poor nutritional state in humans that may increase susceptibility (Hugon et al., 2000).

Pharmacological, neurochemical and electrophysiological studies suggest that L-BOAA neurotoxicity is mediated by the AMPA subtype of glutamate receptors (Künig et al., 1994; Ross et al., 1989). L-BOAA displaces ^{3}H-AMPA from its receptors, and its in vitro neurotoxicity in cortical and hippocampal neurons is attenuated by AMPA antagonists, (Weiss et al., 1989; Nunn et al., 1987). Neuronal hippocampal damage and behavioral changes induced by L-BOAA in mice and rats are antagonized by specific AMPA antagonists but not by antagonists of NMDA receptors (Willis et al., 1994a; Maione et al., 1995). Overstimulation of AMPA receptors results in cellular influx of sodium and calcium ions, ultimately leading to cell degeneration. Toxicity of L-BOAA in rat hippocampus is also attenuated by scavengers of free radicals (Willis et al., 1994b), suggesting a role for oxidative stress in its neurotoxicity. However, as AMPA neurotoxicity is not antagonized by free radical scavengers, additional mechanisms for L-BOAA neurotoxicity may exist, not related to activation of AMPA receptors (Hugon et al., 2000).

4. Alcohols

Methanol and ethanol are two alcohols associated with neurotoxicity. While the latter is a basic component of all alcoholic beverages (wine, beer, liquors), the former can find its way in to some of the same drinks because of illegal practices, when methanol is added to increase alcoholic grade. Large outbreaks of methanol poisoning occurred during prohibition in the USA, among civilian and soldiers during World War II, and in Italy in 1985 (Ludolph, 2000). While minor dietary contributions to methanol exposure are provided by the artificial sweetener aspartame, as well as some fresh fruits and vegetables (Ludolph, 2000), the most prominent route of intoxication is ingestion of methanol in adulterated ethanol-containing liquids. Ingested methanol is rapidly absorbed and metabolized in the liver to formaldehyde and subsequently to formate, the metabolite most likely to be responsible for the neurotoxic effects. Formate is detoxified to carbon dioxide through a folate-dependent pathway, which is more efficient in rodents than in non-human primates and humans. This is likely a major cause of species differences in methanol neurotoxicity, with humans displaying a higher sensitivity (Liesivuori and Savolainen, 1991).

The major target of methanol toxicity is the visual system, in particular the optic nerves. Upon acute methanol intoxication, CNS depression, gastrointestinal disturbances and a severe metabolic acidosis are prominent. This is followed

by an asymptomatic period of 12–24 h, after which visual symptoms develop, including photophobia, cloudy vision, loss of light perception, and perception of spot of flashes. Complete blindness may develop within hours or gradually over several days (Ford and McMartin, 1991). Optic nerves from primates intoxicated with methanol present intra-axonal swelling of microtubules, as well as swelling of oligodendrocytes (Ludolph, 2000). Neurotoxicity is believed to be due to a direct effect of formate, which inhibits the mitochondrial enzyme cytochrome oxidase (complex IV of the mitochondrial chain) resulting in the interruption of ATP production, independent of metabolic acidosis. In fact, formate has been shown to produce ocular toxicity in primates, and correction of metabolic acidosis in methanol-poisoned patients does not necessarily prevent or reverse the development of ocular toxicity (Tephly, 1991). Therapeutic interventions in case of methanol poisoning are only effective if they occur at the very early stages, or they are based on preventing the metabolic formation of formate. For this purpose ethanol is used, as it competes with alcohol and aldehyde dehydrogenases, or, as an alternative, 4-methylpyrazole, an inhibitor of alcohol dehydrogenase (Ford and McMartin, 1991).

In addition to its role as an antidote for methanol poisoning, ethanol, when consumed moderately, may exert a beneficial effect on cardiovascular disease (the so called French paradox). However, acute or chronic consumption of large amounts of ethanol may have significant deleterious effects on the nervous system. Ethanol is metabolized to acetaldehyde and then to acetate by the same dehydrogenases that metabolize methanol, but can also be oxidized to acetaldehyde by cytochrome P4502E1 or by catalase (Otten et al., 2001). Acute ethanol exposure causes euphoria and hyperactivity as a result of disinhibition, followed by signs and symptoms (slurred speech, drowsiness, stupor), due to its CNS depressant action (Charness et al., 1989). Blood ethanol levels (BEL) of 20–80 mg/dl have been imposed as upper limits by most nations for driving a motor vehicle or other machinery, because of the potential for impaired concentration and judgment.

Severe neurotoxic effects can be seen in chronic alcoholics. These include Korsakoff's syndrome, characterized by severe cognitive impairment, with damage to the limbic system and the cerebral cortex; Wernicke's disease, which results from nutritional deficiency of thiamin, and consists in mental abnormalities, abnormal eye movements and gait ataxia; and, in a small number of cases, cerebellar degeneration, with a loss of Purkinje cells and severe ataxia (Otten et al., 2001; Brust, 2000). An alcoholic dementia characterized by cognitive impairment, loss of frontal cortex neurons, reduced brain weight and decreased cerebral blood flow, which cannot be explained by nutritional deficiency has also been described (Harper, 1998). Similar findings have also been reported in animals exposed for an extended period to high doses of ethanol (Fadda and Rossetti, 1998).

An additional, and most relevant, aspect of ethanol neurotoxicity is represented by its effects on the developing brain. Children born from mothers who abuse alcohol during pregnancy often present a syndrome (fetal alcohol syndrome or FAS) whose principal features are CNS dysfunctions (mental retardation, microcephaly and microencephaly, brain malformations), growth deficiencies and particular facial features (Streissguth et al., 1980). The CNS effects of FAS are of particular concern, as they appear to be long-lasting if not irreversible (Spohr et al., 1993). Mental retardation, decreased IQ and other behavioral abnormalities may also be present in the absence of full-blown FAS, and are often referred to as alcohol-related neurodevelopmental disorders (ARND) or fetal alcohol effects (FAE) (Stratton et al., 1996). Animal studies have shown that a direct effect of ethanol on the developing brain is responsible for the CNS abnormalities present in FAS. Though "binge" drinking, leading to very high BEL, is believed to be more deleterious than continuous low exposures, a safe dose of ethanol during pregnancy cannot be established, and abstinence from alcoholic beverages is recommended to pregnant women (Brust, 2000). Exposure to ethanol during brain development has been shown to cause several alterations of neuronal and glial cells. These include neuronal cell loss, due mostly to apoptosis (Miller, 1995; Ikonomidou et al., 2000), as well as alterations in glial cell proliferation and maturation (Guizzetti et al., 1997; Guerri et al., 2001). At the cellular and molecular levels, ethanol has been shown to exert a variety of effects, some of which may contribute to its ability to damage the developing brain. Among these are the inhibition of NMDA receptors, facilitation of GABA-A receptors, inhibition of acetylcholine- and growth factor-activated signal transduction pathways, alterations of neuronal adhesion molecules, and generation of oxidation stress (Crews, 2000).

5. Conclusions

This brief overview indicates that exposure to a number of substances present in the diet can negatively affect the nervous system leading to severe neurotoxicity. The discussion has focused on a limited number of compounds, to underline different aspects of the issues relating to food-borne neurotoxicants to human neurotoxicity. Domoic acid can be present, as a natural contaminant, in shellfish and when safe limits are exceeded, can cause severe excitatory neurotoxicity. L-BOAA is a natural constituent of plants which were, and still are, utilized as a food source in some parts of the world, and can lead to neurolathyrism. Methanol was discussed as an example of how unscrupulous adulteration of food (beverages) can lead to severe human poisoning, while ethanol was chosen as an example of legal and accepted component of the diet that can have deleterious consequences if abused. As stated in the introduction, one should be aware that several other contaminants and/or constituents of the diet can lead to subtle or severe manifestations of neurotoxicity, and perhaps contribute to some human neuropsychiatric and neurodegerative disorders (Candura et al., 1998).

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References

Adams, N., Lesoing, M., Trainer, V., 2000. Environmental influences on domoic acid accumulation in razor clams on the Washington coast. J. Shellfish Res. 19, 1007.

Bleakman, D., 1999. Kainate receptor pharmacology and physiology. Cell. Mol. Life Sci. 56, 558.

Bondy, S.C., Lee, D.K., 1993. Oxidative stress induced by glutamate receptor agonists. Brain Res. 610, 229.

Bose, R., Glavin, G.B., Pinsky, C., 1989. Neurotoxicity and lethality of toxic extracts from Atlantic Coast shellfish. Prog. Neuropsychopharmacol. Biol. Psychiatry 13, 559.

Branchi, I., Capone, F., Alleva, E., Costa, L.G., 2003. Polybrominated diphenyl ethers: neurobehavioral effects following developmental exposure. Neurotoxicology 24, 449.

Brust, J.C.M., 2000. Ethanol. In: Spencer, P.S., Schaumburg, H.H. (Eds.), Experimental and Clinical Neurotoxicology. Oxford University Press, New York, p. 541.

Candura, S.M., Manzo, L., Costa, L.G., 1998. Role of occupational neurotoxicants in psychiatric and neurodegenerative disorders. In: Costa, L.G., Manzo, L. (Eds.), Occupational Neurotoxicology. CRC Press, Boca Raton, p. 131.

Charness, M.E., Simon, R.P., Greenberg, D.A., 1989. Medical progress: ethanol and the nervous system. N. Engl. J. Med. 321, 442.

Clayton, E.C., Peng, Y.G., Means, L.W., Ramsdell, J.S., 1999. Working memory deficits induced by single but not repeated exposures to domoic acid. Toxicon 37, 1025.

Cohn, D.F., Streifler, M., 1981. Human neurolathyrism, a follow-up study of 200 patients. Part I. Clinical investigation. Schweiz Arch. Neurol. Neurochir. Psychiatr. 128, 151.

Coyle, J.T., Puttfracken, P., 1993. Oxidative stress, glutamate, and neurodegenerative disorders. Science 262, 689.

Crews, F.T., 2000. Neurotoxicity of alcohol: excitotoxicity, oxidative stress, neurotrophic factors, apoptosis and cell adhesion molecules. In: Noronho, A., Echardt, M., Warren, K. (Eds.), Review of NIAAA's Neuroscience and Behavioral Research Portfolio. U.S. Dept. of HHS, Bethesda, MD, p. 189.

Dormont, D., 2002. Prions, BSE and food. Int. J. Food Microbiol. 78, 181.

Fadda, F., Rossetti, Z.L., 1998. Chronic ethanol consumption: from neuroadaptation to neurodegeneration. Prog. Neurobiol. 56, 385.

Ford, M.D., McMartin, K., 1991. Ethylene glycol and methanol. In: Ford, M.D., Delaney, K.A., Ling, L.J., Erickson, T. (Eds.), Clinical Toxicology. W.B. Saunders Co, Philadelphia, p. 757.

Goldman, L.R., Koduru, S., 2000. Chemicals in the environment and developmental toxicity to children: a public health and policy perspective. Environ. Health Perspect. 108 (Suppl. 3), 443.

Grunow, W., 1999. Food: compound-related aspects. In: Marquardt, H., Schafer, S.G., McLellan, R.O., Welsch, F. (Eds.), Toxicology. Academic Press, San Diego, p. 1103.

Guerri, C., Pascual, M., Renau-Piqueras, J., 2001. Glia and fetal alcohol syndrome. Neurotoxicology 22, 593.

Guizzetti, M., Catlin, M., Costa, L.G., 1997. Effects of ethanol on glial cell proliferation: relevance to the fetal alcohol syndrome. Front. Biosci. 2, e95.

Gupta, Y.K., Briyal, S., Chaudhary, G., 2002. Protective effect of trans-resveratrol against kainic acid-induced seizures and oxidative stress in rats. Pharmacol. Biochem. Behav. 71, 253.

Hampson, D.R., Manalo, J.L., 1992. Interaction of domoic acid and several derivatives with kainic acid and AMPA binding sites in rat brain. Eur. J. Pharmacol. 218, 1.

Harper, C., 1998. The neuropathology of alcohol-specific brain damage, or does alcohol damage the brain? J. Neuropathol. Exp. Neurol. 57, 101.

Hugon, J., Ludolph, A.C., Spencer, P.S., 2000. β-*N*-oxalylamino-L-alanine. In: Spencer, P.S., Schaumburg, H.H. (Eds.), Experimental and Clinical Neurotoxicology. Oxford University Press, New York, p. 925.

Ikonomidou, C., Bittijan, P., Ishimasu, M.J., Woznick, D.F., Koch, C., Gent, K., Price, M.T., Stefavsko, V., Morster, F., Tenkova, T., Dikranian, K., Olney, J.W., 2000. Ethanol-induced apoptotic neurodegeneration and fetal alcohol syndrome. Science 287, 1056.

Kerr, D.S., Razak, A., Crawford, N., 2002. Age-related changes in tolerance to the marine algal excitotoxin domoic acid. Neuropharmacology 43, 357.

Kessler, A., 1947. Lathyrismus. Monatsschr. Psychiatr. Neurol. 113, 345.

Künig, G., Hartman, J., Niedermeyer, B., Deckert, J., Ramsmayr, G., Heinsen, H., Beckmann, H., Riederer, P., 1994. Excitotoxins L-beta-oxalyl-amino-alanine (L-BOAA) and 3,4,6-trihydroxyphenylalanine (6-OH-DOPA) inhibit [3H] alpha-amino-3-hydroxy-5, methyl1-4-isoxazole-propionic acid (AMPA) binding in human hippocampus. Neurosci. Lett. 169, 219.

Liesivuori, J., Savolainen, M., 1991. Methanol and formic acid toxicity: biochemical mechanisms. Pharmacol. Toxicol. 69, 157.

Lockwood, A.H., 2000. Pesticides and Parkinsonism: is there an etiological link? Curr. Opin. Neurol. 13, 687.

Ludolph, A.C., 2000. Methanol. In: Spencer, P.S., Schaumburg, H.H. (Eds.), Experimental and Clinical Neurotoxicology. Oxford University Press, New York, p. 773.

Maione, S., Berrino, L., Leyva, J., DeNovellis, V., Pallotta, M., Rossi, F., 1995. Behavioral effects induced by microinjection of L-BOOA into the ventrolateral PAG matter of the mouse. Pharmacol. Biochem. Behav. 50, 453.

Marien, K., 1996. Establishing tolerable dungeness crab (cancer magister) and razor clam (siliqua patula) domoic acid contaminant levels. Environ. Health Perspect. 104, 1230.

Mattson, M.P., 2002. Preface. In: Mattson, M.P. (Ed.), Diet–Brain Connections: Impact on Memory, Mood, Aging and Disease. Kluwer Academic Publishers, Boston, p. vii.

Miller, M.W., 1995. Generation of neurons in the rat dentate gyrus and hippocampus: effect of prenatal and postnatal treatment with ethanol. Alcohol Clin. Exp. Res. 19, 1500.

Miyamoto, M., Coyle, J.T., 1990. Idebenone attenuates neuronal degeneration induced by intrastriatal injection of excitotoxins. Exp. Neurol. 108, 38.

Mos, L., 2001. Domoic acid: a fascinating, marine toxin. Environ. Toxicol. Pharmacol. 9, 79.

Nunn, P.B., Seelig, M., Zagoren, J.C., Spencer, P.S., 1987. Stereospecific acute neuronotoxicity of "uncommon" plant aminoacids linked to human motor-system diseases. Brain Res. 410, 375.

Otten, E.J., Prybys, K.M., Gesell, L.B., 2001. Ethanol. In: Ford, M.D., Delaney, D.A., Ling, L.J., Erickson, T. (Eds.), Clinical Toxicology. Philadelphia, W.B. Saunders Co, p. 605.

Perl, T.M., Bedard, L., Kosatsky, T., Hockin, J.C., Todd, E.C.D., Remis, R.S., 1990. An outbreak of toxic encephalopathy caused by eating mussels contaminated with domoic acid. N. Engl. J. Med. 322, 1771.

Puttfarcken, P.S., Getz, R.L., Coyle, J.T., 1993. Kainic acid-induced lipid peroxidation: protection with buylated hydroxytouluene and U78517F in primary cultures of cerebellar granule cells. Brain Res. 624, 223.

Ross, S.M., Roy, D.N., Spencer, P.S., 1989. β-*N*-oxalylamine-L-alanine. Action on glutamate receptors. J. Neurochem. 53, 710.

Scallet, A.C., Binienda, Z., Caputo, F.A., Hall, S., Paule, M.G., Roundtree, R.L., Schmued, L.C., Sobotka, T.J., Slikker, W., 1993. Domoic-acid treated cynomolgus monkeys (*M. fascicularis*): effects of dose on hippocampal neuronal and terminal degeneration. Brain Res. 627, 307.

Sharp, D., 2003. Acrylamide in food. Lancet 361, 361.

Sobotka, T.J., Brown, R., Quander, D.Y., Jackson, R., Smith, M., Long, S.A., Barton, C.N., Rountree, R.L., Hall, S., Eilers, P., Johannessen, J.N., Scallet, A.C., 1996. Domoic acid: neurobehavioral and neurohistological effects of low-dose exposure in adult rats. Neurotoxicol. Teratol. 18, 659.

Spencer, P.S., Ludolph, A.L., Duivedi, M.P., Roy, D.N., Hugon, J., Schaumburg, H.H., 1986. Lathyrism: evidence for the role of the neuroexcitatory amino acid BOAA. Lancet ii, 1066.

Spencer, P.S., 1999. Food toxins, AMPA receptors and motor neuron diseases. Drug Metab. Rev. 31, 561.

Spohr, M.L., Williams, J., Steinhausen, H.C., 1993. Prenatal alcohol exposure and long term developmental consequences. Lancet 341, 907.

Steuerwald, U., Weihe, P., Jorgensen, P.J., Bjerve, K., Brock, J., Heinzow, B., Budtz-Jorgensen, E., Grandjean, P., 2000. Maternal seafood diet, methylmercury exposure, and neonatal neurologic function. J. Pediatr. 136, 599.

Stewart, G.R., Zorumski, C.F., Price, M.T., Olney, J.W., 1990. Domoic acid: a dementia-inducing excitotoxic food poison with kainic acid receptor specificity. Exp. Neurol. 110, 127.

Stratton, K., Howe, C., Battaglia, F. (Eds.), 1996. Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention and Treatment. National Academy Press, Washington, D.C, p. 213.

Streissguth, A.P., Landewsman-Dwyer, S., Martin, J.C., Smith, D.W., 1980. Teratogenic effects of alcohol in human and laboratory animals. Science 209, 353.

Sun, A.Y., Cheng, Y., Bu, Q., Oldfield, F., 1992. The biochemical mechanisms of the excitotoxicity of kainic acid. Mol. Chem. Neuropathol. 17, 51.

Sutherland, A.P., Hoesing, J.M., Whishaw, I.Q., 1990. Domoic acid, an environmental toxin, produces hippocampal damage and severe memory impairment. Neurosci. Lett. 120, 221.

Teitelbaum, J.S., Zatorre, R.J., Carpenter, S., Gendron, D., Evans, A.C., Gjedde, A., Cashman, N.R., 1990. Neurologic sequelae of domoic acid intoxication due to the injection of contaminated mussels. N. Engl. J. Med. 322, 1781.

Tephly, T.R., 1991. The toxicology of methanol. Life Sci. 48, 1031.

Truelove, J., Iverson, F., 1994. Domoic acid clearance and clinical observations in the cynomolgus monkey and Sprague Dawley rat following a single i.v. dose. Bull. Environ. Contam. Toxicol. 52, 479.

Tryphonas, L., Truelove, J., Iverson, F., 1990a. Acute parenteral neurotoxicity of domoic acid in cynomolgus monkeys (*M. fascicularis*). Toxicol. Pathol. 18, 297.

Tryphonas, L., Truelove, J., Nero, E., Iverson, F., 1990b. Acute neurotoxicity of domoic acid in the rat. Toxicol. Pathol. 18, 1.

Weiss, J.H., Koh, J.H., Choi, D.W., 1989. Neurotoxicity of β-*N*-methylamino-L-alanine (BMAA) and β-*N*-oxalylamino-L-alanine (BOAA) on cultured cortical neurons. Brain Res. 497, 64.

Willis, C.L., Meldrum, B.S., Nunn, P.B., Anderton, B.H., Leigh, P.N., 1994a. Neuronal damage induced by β-*N*-oxalylamine-L-alanine in the rat hippocampus can be prevented by a non-NMDA antagonist, 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F) quinoxaline. Brain Res. 627, 55.

Willis, C.L., Meldrum, B.S., Nunn, P.B., Anderton, B.H., Leigh, P.N., 1994b. Neuroprotective effect of free radical scavengers on beta-*N*-oxalylamino-L-alanine (BOAA)-induced neuronal damage in rat hippocampus. Neurosci. Lett. 182, 159.

Winneke, G., Walkowiak, J., Lilienthal, H., 2002. PCB-induced neurodevelopmental toxicity in human infants and its potential mediation by endocrine dysfunction. Toxicology 181/182, 161.

Xi, D., Peng, Y.G., Ramsdell, J.S., 1997. Domoic acid is a potent neurotoxin to neonatal rats. Nat. Toxins. 5, 74.

Zaczek, R., Coyle, J.T., 1982. Excitatory amino acid analogues: neurotoxicity and seizures. Neuropharmacology 21, 15.