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The Cellular Effect of Lead Poisoning and Its Clinical Picture

Robert Brochin[1], Siena Leone[2], Dylan Phillips[1], Nicholas Shepard[1], Diane Zisa[1], & Allan Angerio, PhD[1]

Department of Human Science[1], Department of International Health[2]
Georgetown University
School of Nursing and Health Studies

Abstract

Lead intoxication affects many systems of the body including the cardiovascular, renal, and reproductive systems. Its most detrimental effects occur in the nervous system, where lead blocks the receptor know as N-methyl-D-aspartate, an effective receptor involved in the maturation of brain plasticity. The toxicity of lead plays a major role in the communication between astrocytes and endothelial cells. By disrupting the blood-brain barrier, it causes encephalopathy and edema that primarily affects the cerebellum. Fetus' astrocytes in utero are at an especially high risk of lead intoxication because the immature endothelial cells that form the capillaries of the brain offer a decreased resistance to lead, and thereby easily allow Pb2+ to enter the brain. Intracellularly, lead replaces calcium as a second messenger, binding with calmodulin more readily than calcium, resulting in an alteration in protein conformation. This altered conformation leads protein kinases to phosphoylate and activate substrate molecules, which alter various cellular processes leading to the clinical picture of lead poisoning. In order to prevent the deleterious effects that Pb2+ has on the human system, it is important to understand the various means by which it is introduced into the body. Environmental and domestic sources of Pb2+ are the most often seen causes for the disease, but with proper precautionary measures, it is easily possible to adequately reduce the level of risk associated with lead poisoning.

Lead's Effect on CNS

Lead intoxication can affect many systems of the body, including the cardiovascular, renal, and reproductive systems. However, lead has its most detrimental and serious effects on the central nervous system. In the nervous system, lead blocks the receptor know as N-methyl-D-aspartate, an effective receptor involved in the maturation of brain plasticity, which are changes that occur in brain organization. The blockage of this receptor in the brain leads to the interruption of long-term potentiation, which, in turn, limits the permanent intake and storage of newly learned knowledge. Also, elevated blood lead levels (BLLs) impair the blood-brain barrier function (1).

The blood-brain barrier is made up of many endothelial cells connected by tight junctions. These endothelial cells become surrounded by astrocytes, which actually outnumber neurons in brain; in the process, the astrocytes weave their way in between the axons and dendrites. Studies have shown that the toxicity of lead plays a major role in the communication between the astrocytes and the endothelial cells (1). The blood-brain barrier has a very important function in maintaining the fluid environment of the nervous system. While other organs in the body transport molecules by the simple method of diffusion, the blood-brain barrier is very persnickety in that it selects only certain and essential water-soluble molecules (essential amino acids, glucose, calcium, sodium, and potassium) to be transported by carriers in the plasma membrane. This intricacy in the transportation of molecules through the blood-brain barrier explains the barrier's susceptibility to trauma due to dangerous toxicants (see Figure 1) (2).

When the blood-brain barrier is exposed to high levels of lead concentration, plasma moves into the interstitial spaces of the brain, resulting in edema. High blood lead toxicity of the CNS results in encephalopathy and edema that mainly affects the

cerebellum of the brain (3). Edema causes extreme pressure increases in the brain, which can lead to irreversible brain damage (4). This type of brain damage includes decreased attention, affects visual-motor reasoning skills and social behavior and can damage mathematic skills and reading abilities (5). Studies have also shown that lead intoxication drastically decreases cognitive ability, resulting in a loss of IQ points anywhere from 0 to 5 per increase of 10 μg/dl in BLLs (6). This will be discussed further below.

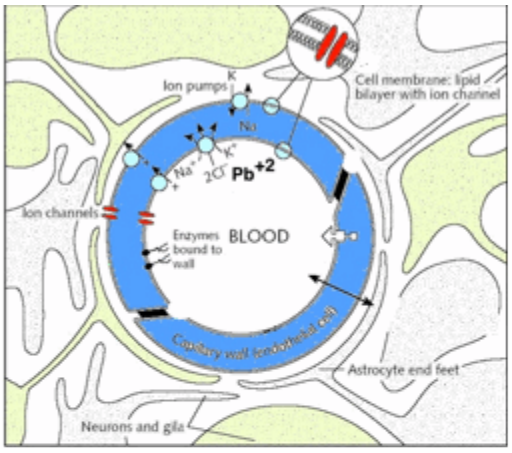


Figure 1-Lead's movement through the blood brain barrier.
Lead ions are able to permeate the blood brain barrier via ion channels. Lead interferes in the communication between astrocytes and endothelial cells. Modified from: http://content.answers.com/main/content/img/oxford/Oxford_Body/019852403x.blood-brain-barrier.1.jpg

Lead's Effect on Other Systems

Briefly looking at the other systems of the body further reveals the detrimental effects of lead. Recent studies have shown that even low levels of lead exposure can also affect the renal system. Low BLLs lead to nephropathy of the kidneys as well as hypertension, gout, and future kidney failure (2). Nephropathy of the kidneys exists in three forms, as follows: acute lead poisoning, chronic lead nephropathy, and lead hypertension (6). Lead toxicity also affects the reproductive system in both genders. In males, sperm count is drastically decreased while the abnormal occurrence of sperm increases; in females, lead toxicity can create adverse outcomes in pregnancy. Recent studies also demonstrate that the cardiovascular system is just as affected by acute and chronic levels of lead as any other system in the body. These studies have shown myocardial morphologies, irregular systolic and diastolic numbers, as well as ECG disturbances (2).

Lead's Alteration of Second Messenger Systems

On a cellular level, numerous research studies support the hypothesis that lead has an effect on altering cellular second messenger systems. Second messenger systems usually involve nonsteroid hormones, such as amines proteins, and peptides. These hormones target specific receptor sites on cells' surfaces known as binding sites, which cause the activation of cell membrane proteins. The hormone that initially causes a change in the activity of cell membrane proteins is known as a first messenger, and the biochemicals within the cell that cause changes that are the expression of the hormone are known as second messengers (8). Research has shown that lead can replace calcium (Ca2+), perhaps the most ubiquitous second messenger, and alter the function of the cell.

Intracellular concentrations of Ca2+ generally increase in one of two ways: the opening of calcium channels in the cell membrane or the release of stored calcium in the endoplasmic reticulum. Both of these are results of the stimulation of a G-protein. In the case of the former, once a first messenger binds to a binding site, a G-protein, attached to the cell membrane, but facing the inside of the cell, is activated. This G-protein then stimulates the opening of the calcium channel (9). Extracellular calcium then enters the cell and combines with calmodulin, a calcium-binding protein, which affects and stimulates many intracellular functions such as inflammation, metabolism, apoptosis, muscle contraction, intracellular movement, nerve growth and immune response. Lead can interfere with both pathways (10).

Lead has a high affinity towards calmodulin and is able to bind to it even at low levels. In a study researching lead's ability to bind to CaM (calmodulin), it was determined that calcium binding sites are accessible to lead ions in the crystal state, and in fact, lead has a higher affinity for CaM binding sites than calcium does. These observations can be explained, at least in part, by the variations in the ionic radii of the bonds formed by these ions. The normal bond distance between Ca2+ and protein O atoms is 2.3Å, while the

distances in the Pb2+ complex vary between 2.0 and 2.7 Å, demonstrating that lead ions have the ability to create shorter and therefore stronger bonds with the protein complex (11).

Lead ions are also more effective than calcium ions in supporting CaM-dependent phosphorylation of brain proteins and the binding of calmodulin to brain proteins. Calmodulin has four Ca2+ binding sites. Pb2+ not only binds to these, but also to a "second class" of calmodulin binding sites, to which calcium does not bind. The binding of lead ions at these sites alters protein conformation (12). This is what may cause an altered effect on the activation of protein kinases. Protein kinases transfer phosphate groups from ATP molecules to protein substrate molecules; this phosphorylation alters the shape of the substrate molecules and converts them from inactive to active forms. The activated proteins then alter various cellular processes such as further activating enzymes, altering membrane permeability, promoting synthesis of certain proteins, stimulating or inhibiting metabolic pathways, and initiating secretion of hormones and other substances (8). When protein kinases are inappropriately activated—as they are when lead binds to calmodulin instead of calcium—any of these cellular processes may be disrupted. According to one study, acute and chronic exposure to lead would predominantly affect two specific protein complexes: protein kinase C and the N-methyl-D-aspartate subtype of glutamate receptor, mentioned above. These protein complexes are deeply involved in learning and cognitive functions and are also thought to interact significantly with each other to mediate these functions (13).

A study of lead and calcium uptake in bovine adrenal medullary cells has revealed ways in which lead serves to alter the function of calcium. The depolarization of a cell membrane, caused by the G-protein, opens calcium channels. Lead inhibits calcium entry, and the depolarization also stimulates lead entry. The channel has an extremely high permeability for lead ions, in the range of about ten times that of its permeability for calcium ions. Normally, these channels readily close after calcium passes through due to an internal effect of the calcium ions. However, with lead, the channels do not inactivate because of the absence of this internal effect (12). Once lead is in the cytoplasm of the cell, the above abnormal processes may proceed (see Figure 2).

Lead's Effect In Utero

Perhaps the most crucial and detrimental period when one may experience lead poisoning is the in utero period. During the in utero period, the fetus is at an increased susceptibility to toxins and disease since it is in the process of developing, and is therefore unable to adequately protect itself. Lead exposure during this period can lead to severe neurological and developmental problems that may manifest themselves later in the affected child's life. Although there may not be an immediate presentation of these symptoms, it is believed that a child who has been subject to lead exposure in utero will most likely develop severe malfunctions in their central nervous system sometime in the future (14). During gestation, lead has the ability to easily cross from the mother's bloodstream to the fetus via the placenta (15). The mechanism for this transport of lead, however, is not clearly known. There have been strong correlations between mother blood level and cord blood levels, as well as a linear relationship between the transfer of lead and umbilical cord blood flow rate. Both of these findings indicate that lead transport via the placenta may be a simple case of diffusion. An alternate proposal, however, is that lead in fetal tissue may be affected by calcium transport and intracellular calcium metabolism (16). In both instances, the mother's blood is the source for exposure. The lead present in the mother's blood during the pregnancy may have come from bone, where a majority of lead is stored, or from the environment. Even if the mother's blood lead levels range from 1 µg/dl to 6 µg/dl, which is well below the 10 µg/dl that the Center for Disease Control and Prevention has established as the level for concern, there can be deleterious effects on the neonate (17).

One of the main components of the CNS, the brain, is at an especially high risk of susceptibility to lead toxicity during in utero. During , the blood-brain barrier begins its development and continues to develop until approximately six weeks after birth (18). Thus, lead exposure in utero is especially dangerous since the blood-brain barrier is not fully developed and offers little protection for the brain. Furthermore, there has been experimental evidence that suggests that the fetal brain offers low resistance to lead toxicity because it lacks lead-protein complexes in astryocytes that remove lead from the mitochondria. These astrocytes are at an especially high risk of lead toxicity during in utero since the immature endothelial cells

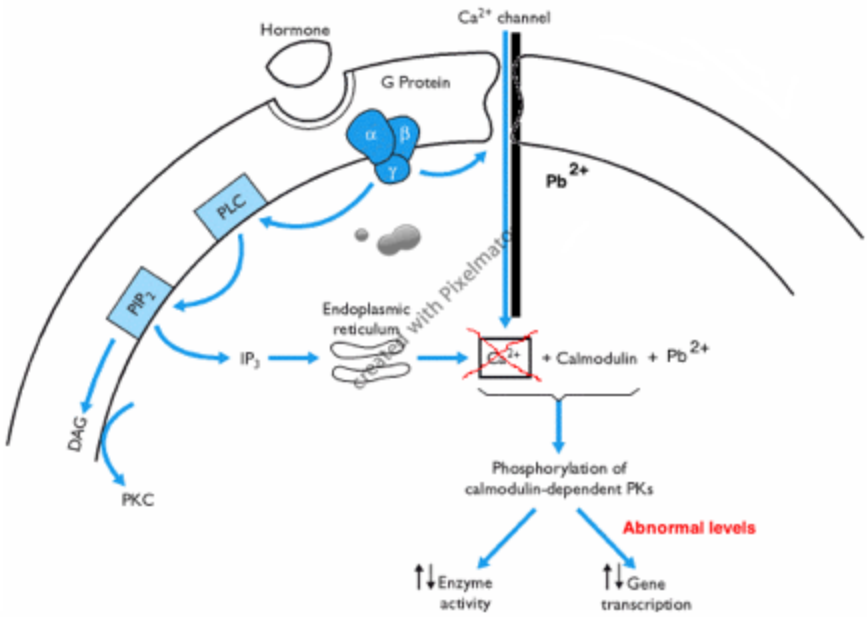


Figure 2
Pb^{2+} enters the cell through an open Ca^{2+} channel (stimulated by a G-protein) and binds with calmodulin more readily than does calcium. It then cause the phosphorylation of dependent protein kinases leading to abnormal enzyme activities and gene transcription.
In an alternative route, the G-protein activates Phospholipase C (PLC) which in turn activates the hydrolysis of phosphotidylinositol 4,5-bisphosphate (PIP_2) to inositol trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 normally releases stored Ca^{2+} that combines with calmodulin, but in the case where lead is stored in cell organelles IP_3 may stimulate the release of Pb^{2+} to combine calmodulin.
*Modified from Figure 1 in citation 9.

that form the capillaries of the brain offer a decreased resistance to lead, and thereby easily allow fluids and ions, such as Pb2+, to enter the brain (20).

A child's CNS is at a much higher risk of injury or disease than that of a developed adult's due to the fact that a child's CNS is still developing. Lead toxicity during this developmental period has often been associated with cognitive impairment and learning malfunctions, as lead can accumulate in their nervous systems as they develop. At a microscopic level, this may be due to lead's suppression of N-methyl--aspartate (NMDA). NMDA receptors are amino acid receptors that play an important role in brain development and synaptic plasticity, especially in regards to the long-term potentiation of the hippocampus (20). Lead exposure during the developmental years and its inhibition of NMDA receptors has been attributed to a decrease in IQ that ranges with varying blood lead levels (6, 22, 23).

Lead Poisoning in Children

Currently, about 3% of children in the U.S. have elevated blood levels of lead (>10 µg/dl). However, recent data shows that effects on cognitive skills in children could occur at lower levels, even as low as 5 µg/dl. If this is used as the threshold, then as much as 26% of U.S. children could be harmed by lead poisoning (4).

The most widely studied effect of lead poisoning is the damage it does to cognitive abilities. About ¼ to ½ of an IQ point is lost per 0.04826 mcmol/L increase in blood lead levels during the preschool years. The IQ loss is permanent, as the relationship held true after ten years with a group of 2 year olds (24). Another study estimates an IQ deficit of 0 to 5 points for every 10 µg/dl increase in blood lead levels, as previously mentioned (5). The children usually lose about 5-7 IQ points. The loss of cognitive ability is associated with shortened attention span and antisocial behavior. In

order for the effects to become permanent, the child must be exposed to unsafe levels of lead while they are under two years old, after which the effects appear to be reversible (2).

Clinical Presentations

As previously discussed, children are extremely vulnerable to the negative effects of lead exposure mainly because of the damage this metal causes on the nervous system during a crucial time in the child's development. Although it is more common to see lead poisoning in children, adults are not immune from such damage (25). A very high risk is associated with women of childbearing age who possess high levels of lead in their bodies before pregnancy. This lead eventually affects the fetus through the placenta, which connects the mother and the fetus, and has the potential to cause fetal brain damage or even death of the fetus (see Figure 3) (25). In other adults, exposure to lead manifests itself with numerous problems, including high blood pressure, fertility and digestive problems and muscle and joint pain. Lead affects the nervous system of adults in ways similar to its affect on that of children, leading to problems with memory and concentration (25). In a study conducted to determine the effect past long-term exposure to high levels of lead in the environment has on cognitive ability of older adults, it was found that environmental exposures to lead "may have persistent effects on cognitive function" (26). Another study also related decline in cognitive function of adults to exposure to lead, stating, "Our data suggests that a significant proportion of what is considered to be 'normal' age-related cognitive decline may, in fact, be due to past exposure to neurotoxicants such as lead" (27). Thus, although lead poisoning in adults has been of little concern in the past, it is imperative that adults take precautions in order to avoid the harm that lead inflicts upon systems of the adult body.

Lead poisoning can also present clinically in adults or children in anemia. Lead can affect the formation of heme, causing microcytic anemia. Lead bonds with the sulfhydryl group of proteins, causing impaired function. Delta-aminolevulinic acid dehydratase, which catalyzes the formation of the porphobilinogen ring, and ferrochelatase are both impaired by lead. Low lead levels have been connected to kidney decline in renal function. Lead may play a role in Parkinson's disease and amyotrophic lateral sclerosis. It has been hypothesized that the lack of enzymes with heme may disrupt energy metabolism (see Figure 4 for further clinical presentation) (2).

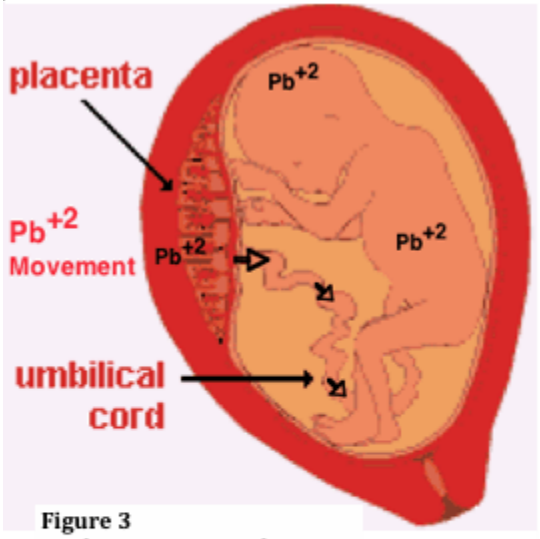


Figure 3
Lead movement into fetus. Lead in mother's blood enters fetus through the placenta and umbilical cord through passive transport. Lead ions eventually infiltrate the blood brain barrier leading to cognitive impairment.
Modified from:
http://anthro.palomar.edu/blood/images/fetus_in_utero.gif

Sources of Lead Exposure

We have seen the effects of lead clinically and on cells, but it also important to consider how humans are exposed to lead. Lead poisoning comes from a variety of different sources. Prior to 1995, a major source was lead solder in the joints of canned food. Lead solder is no longer used in the U.S. but some countries continue to use it. Currently, the primary source of lead ingestion is from lead in paint. In 2002, it was reported that 38 million US households contained lead paint, and 65% of those had a significant lead based paint hazard (5).

Lead poisoning can also come from drinking water. The water may be contaminated at the source from the environment, or in the pipes that carry the water, which can be made of lead, or have lead components. A recent study estimated that 18% of households here

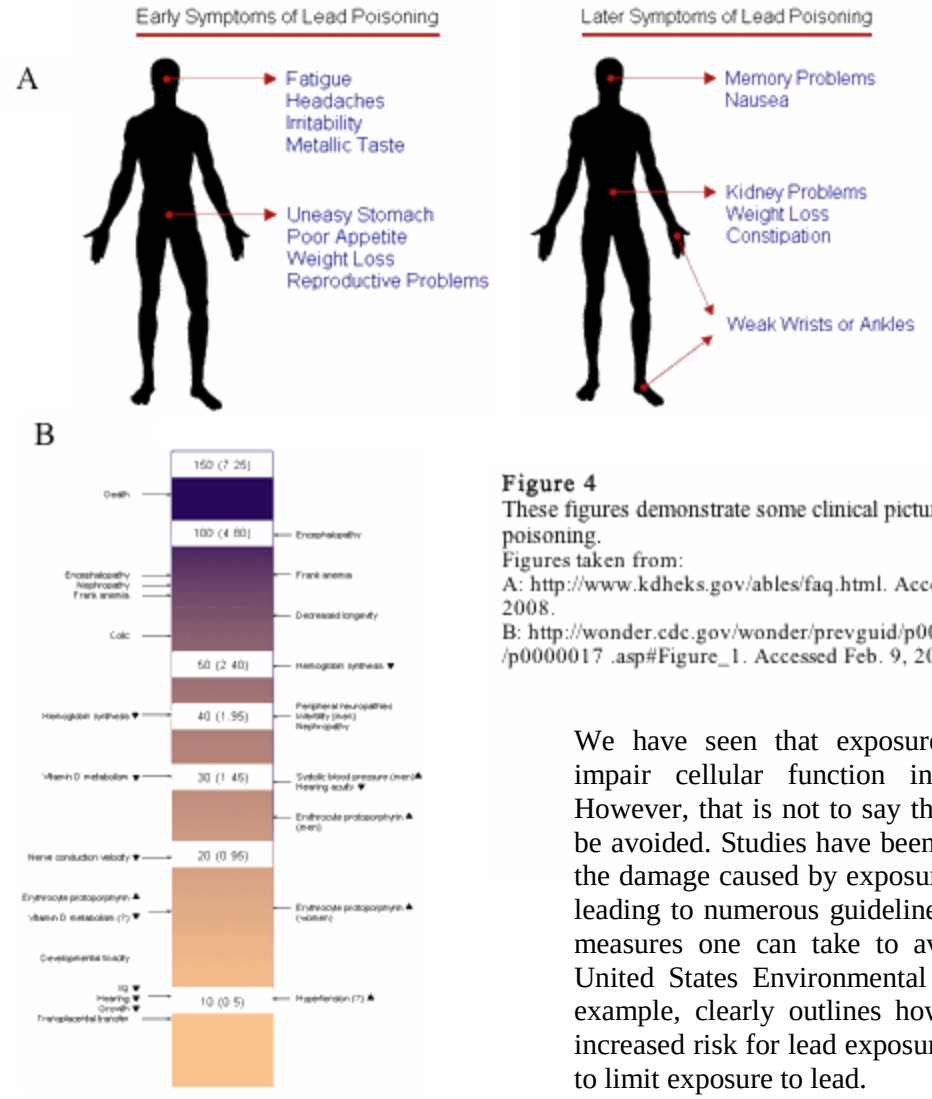


Figure 4
These figures demonstrate some clinical pictures of lead poisoning.
Figures taken from:
A: http://www.kdheks.gov/ables/faq.html. Accessed Feb. 9, 2008.
B: http://wonder.cdc.gov/wonder/prevguid/p0000017 /p0000017 .asp#Figure_1. Accessed Feb. 9, 2008.

in the DC area have had lead service pipes, and 30% of residents in theses houses had blood lead levels greater than 5 µg/dl, which is known to be high enough to cause cognitive defects in children (5).

The combustion of leaded gasoline in the US between 1923 and 1986 is estimated to have put out 4 million tons of lead into the atmosphere and soil, accounting for 90% of lead deposited in the atmosphere (5). Various regulations have reduced the amount of lead used in industry. Now, paint cannot contain more than .06% lead by weight (down from 50%) and gasoline can have no more than 0.1g/L (down from 1.5g/L) (24).

Preventing Lead Poisoning

We have seen that exposure to lead can severely impair cellular function in people of all ages. However, that is not to say that such exposure cannot be avoided. Studies have been conducted to document the damage caused by exposure to high levels of lead, leading to numerous guidelines and lists of protective measures one can take to avoid such damage. The United States Environmental Protection Agency, for example, clearly outlines how to check if one is at increased risk for lead exposure and what steps to take to limit exposure to lead.

The first step in preventing the harm caused by lead is understanding the various ways lead can enter one's system. It is possible to breathe in lead dust directly, put one's hands or other objects covered with lead dust into one's mouth, or eat paint chips or soil that contain lead. Other sources of lead include drinking water if one's home contains lead plumbing, one's job if he or she works with lead, old painted toys and furniture, and hobbies, such as making pottery or stained glass (25). All of these interactions with lead give rise to increased levels of lead in the body, which as previously mentioned, causes serious health problems, especially in children.

To protect one's family, the EPA suggests getting a paint inspection and risk assessment of the home to determine if the home has any lead hazards, including

chipping, peeling, or cracking lead-based paint, lead dust, or lead in the soil surrounding the home. It is important for people to consider that the older their homes are, the more likely they are to contain lead-based paint, since the federal government did not ban the use of such paint until 1978. It is key to hire trained and certified professionals to conduct these inspections (25).

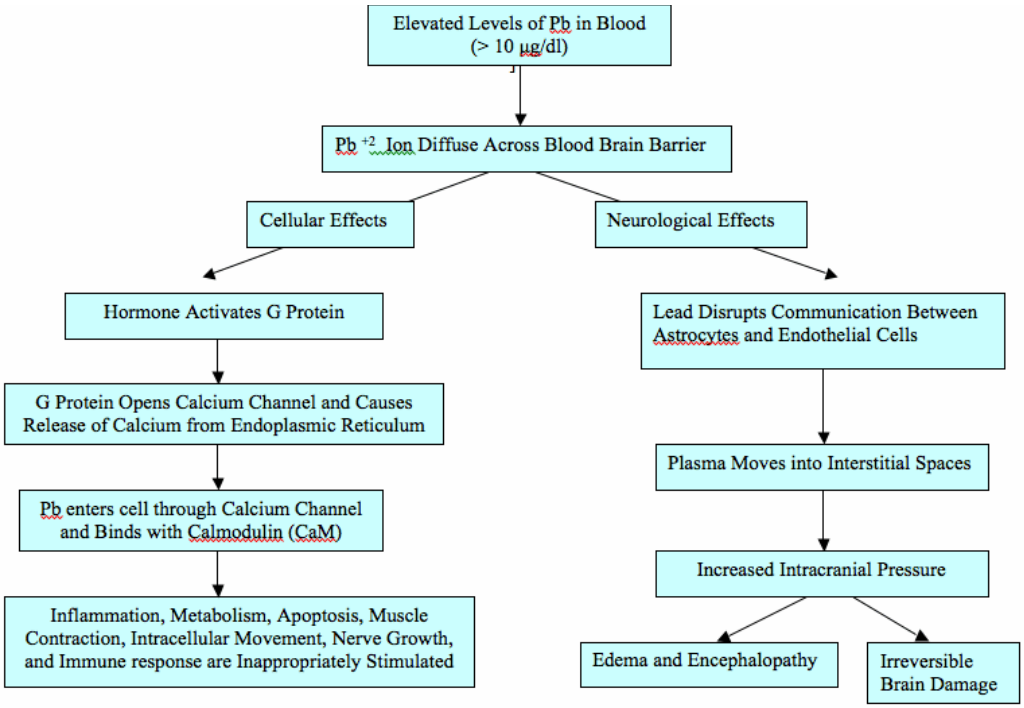
However, one does not need to be a trained professional to take daily measures to prevent lead poisoning. The EPA recommends notifying a landlord immediately if you suspect deteriorating paint in your rented home or apartment. It also suggests cleaning surfaces such as floors and windowsills weekly and carefully cleaning the cleaning utensils used (25). It is vital to take precautions before remodeling one's home because disturbing surfaces with lead-based paint can result in dangerous amounts of lead dust throughout the home. Therefore, it is important that one does not attempt to remove lead-based paint without the help of a trained professional because if not done properly, large amounts of lead dust can be released into the air. In regards to children, washing their hands often, keeping play areas clean, and preventing children from chewing on painted surfaces such as window sills and furniture can limit lead exposure (25). Feeding children balanced diets is also key since "children with good diets absorb less lead" (27). Additionally, insisting that the whole family remove their shoes before entering the home is critical to prevent lead from the soil from entering the home.

The most important step to take if you believe your child has been exposed to lead is to get that child checked. A simple blood test can make a significant difference in protecting children from lead's harmful effects (25). The EPA provides a toll free number for people to ask all questions and receive important tips regarding reducing lead hazards in the home or what to do in case of emergency. Hopefully, with knowledge of these preventative measures, people can strive to make childhood lead poisoning less of an environmental health concern in coming years.

Conclusion

Although preventable, lead poisoning is still a prevalent and extremely detrimental disease that affects many major organ systems. Through its disruption of ubiquitous intracellular second messenger systems (see Figure 5 for summary), it can particularly affect the function of the central nervous system, whose protection should be of primary importance.

Figure 5: Effects Of Increased Lead Blood Levels



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