

Acetylcholines, Toxins and Human Behavior

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Abstract

Interactions between heavy metal toxins have been linked to increased rates of violent crime, with effects exacerbated by dysfunctional acetylcholinesterase. Such interactive effects of neurotoxins are also linked to behavioral dysfunctions including learning failures and substance abuse. This complexity requires further exploration based on more precise understanding of acetylcholine and its regulation by acetylcholinesterase along with other risk factors that undermine behavioral self-control.

Introduction

Neurotoxicology & public policy

To understand many problems among today's school children, it will be essential to transcend the academic barriers between cognitive neuroscience, environmental science, toxicology, psychology, and special education. The human brain is an exceptionally complex biochemical system that is easily damaged by toxic chemicals, yet public policy planners are rarely aware of the extent of the dysfunctions that can be explained by integrating new biological findings in the analysis and treatment of behavioral and learning deficits.

The condition known as Attention Deficit Hyperactivity (ADHD) is perhaps the best known instance of a widespread challenge to educational success. Actually, ADHD is a "spectrum disorder" with a range of symptoms, with some cases primarily marked by "attentional deficits" (which can be due to what has been called sensory "overload" due to hypersensitive responses to sounds and sights) while others are marked primarily by exceptional physical energy and activity [1]. While many cases run in families and seem to be genetic and other factors including gender and parental behavior may influence the likelihood of hyperactivity [2], heavy metals provide an important example of the role of neurotoxins in ADHD.

As a political scientist, I have no claim to expertise on the precise chemistry and biochemistry of these effects and those discussed below. Rather, this essay is an attempt to indicate how several toxins are the byproducts of water treatment chemistry not hitherto studied for its neurotoxic effects on over 160 million Americans need extensive further study: pending such research, our published evidence of harmful outcomes justifies an immediate moratorium on silicofluoride use for the purpose of adding fluoride to water.

Neurotoxins, Acetylcholine and Cognition

The deleterious effects of lead on cognition have long been known [3]. As Benjamin Franklin [4] noted, "the Opinion of this mischievous Effect from Lead is at least above Sixty Years old, and you will observe with Concern how long a useful Truth may be known and exist, before it is generally received and practiced on." More recent research shows that harmful effects occur at blood lead levels below what was once thought to be the "threshold" of 10 µg/dL [5,6]. Less well known is the parallel harm due to excessive levels of manganese [7-9]. The combination of these toxins has worse effects than either separately with implications transcending educational deficits, since both lead (presumably due to its effects on dopamine function) [10] and manganese (which has comparable effects on serotonergic function) [11] have been implicated in violent behavior. Tests of numerous samples of individual violent

offenders show higher burdens of these toxins than comparable non-violent offenders and controls (Tables 1,2) [12]. Moreover, controlling for socio-economic, demographic, and ethnic factors, environmental releases of lead and manganese are highly significant factors in geographic differences in violent crime (Table 3). These findings, which clearly show the interactions of "nature" and "nurture," [13,14] should hardly be surprising insofar as lead is associated with a higher risk of hyperactivity during childhood, and childhood ADHD is predictive of adult criminality [15].

Neurotoxins

Exposure to these toxins is widespread not only in communities with old housing or high levels of lead in the water supply (as was recently found in Washington D.C. and other cities), but at sites of industrial pollution with lead or manganese (such as in the tailings and wastes from mining). Where many children have absorbed multiple toxins, the consequences include learning disabilities, poor behavioral control, and asthma. Yet despite the widespread presence of these harmful effects, policy-makers continue to ignore the connection between environmental pollution and education. For example, unpublished data from standardized tests in Massachusetts indicate that, for seven different subjects and grades, the average score in a community is always more strongly influenced by the percentage of children with over 10 µg/dL of lead in their blood than by any other socio-economic or demographic factor [16]. To put it bluntly, "No Child Left Behind" often amounts to "Poison the children and blame the teachers" (which isn't fair to either children or teachers) [17].

In addition to the dangers of absorbing lead or manganese, the implications of other recent findings in brain chemistry and cognition need to be more widely known. This is especially important since cell imaging now makes it possible to represent visual the types of interactions between brain chemistry and neuronal activity that underly this analysis (Figures 1,2).

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Element	Pihl & Ervin ⁵	Marlow, et al. ⁶	Gottschalk, et al. #1 ⁸	Gottschalk et al. #2 ⁸	Gottschalk et al. #3 ⁸	Schauss et al. ⁷	Schrauzer, et al. ¹³
Lead	2.31 ^{***}	2.38 [*]	1.66	NS	NS	Sig. ^{**}	NS
Cadmium	1.50 ^{***}	2.06 [*]	0.68	NS	NS	Sig. ^{**}	NS
Manganese	1.04	1.50	7.33 ^{***}	3.39 ^{***}	2.15 ^{**}	0.78	2.28 ^{**}
Chromium	NS	1.14	NS	NS	NS	NS	NS
Sodium	1.33	1.41	NS	NS	NS	NS	NS
Mercury	NS	1.41 [*]	NS	NS	NS	NS	NS
Silicon	NS	1.26 [*]	NS	NS	NS	NS	NS
Copper	0.95	2.07 [*]	NS	NS	NS	Sig. ^{**}	NS
Cobalt	0.91	1.39	NS	NS	NS	NS	NS
Lithium	NS	0.58 [*]	NS	NS	NS	NS	0.28 ^{***}
Calcium	0.87	NS	NS	NS	NS	NS	1.14
Magnesium	0.73	NS	NS	NS	NS	NS	0.64
Potassium	1.33	NS	NS	NS	NS	NS	NS
Iron	0.95	NS	NS	NS	NS	NS	NS
Zinc	0.97	NS	NS	NS	NS	NS	NS

* p < .05 ** p < .01 *** p < .0005 NS = Not Significant

NOTE: Comparable data on learning disabled children reveals significantly higher levels of lead (ratio 5.75*), cadmium (ratio 1.59*), manganese (ratio 1.43*), chromium (ratio 2.78*) and sodium (ratio 1.78*), and lower levels of cobalt (ratio .70*) and lithium (ratio .55*). Source: Bryce-Smith D. "Lead Induced Disorder of Mentation in Children." *Nutrition and Health*. 1983; 1: 179-194.

Table 1: Element Levels in Hair of Violent Offenders Ratio of Violent / Control [16]

Independent variables	Ages	Number of juvenile offenses, ages 7-17	Seriousness of juvenile offenses, ages 7-17
Pregnancy and delivery conditions	Birth	NS	NS
Mother's education	Birth	NS	NS
Father's education	Birth	NS	NS
Family income	Birth	NS	NS
Time father unemployed	Birth	0.179 ^{***}	0.115 ^{**}
Hand preference	1	NS	NS
Stanford-Binet	4	NS	NS
Hand preference	4	NS	NS
Eye preference	4	NS	0.059 ^{**}
Foot preference	4	NS	NS
Neurological abnormalities	7	NS	NS
Abnormal movements	7	NS	NS
Abnormal Vision	7	NS	NS
Lead Intoxication	7	0.149 ^{***}	0.143 ^{**}
Anemia	7	NS	0.044 [*]
Intellectual Status	7	NS	NS
Speech	7	0.045 [*]	NS
Foster Parents	7	NS	NS
Father Absence	Birth-7	NS	NS
Household moves	Birth-7	0.092 [*]	0.112
Persons supported	7	NS	0.09 ^{**}
Family income	7	NS	NS
r ²		.157	.128

(n = 487) * p < .05 ** p < .01 *** p < .0005 NS = Not Significant

Table 2: Factors Predicting Juvenile Delinquency, Males in Philadelphia Biosocial Study (source: ref. 16).

Acetylcholine

The report by Furey, Peitri and Haxby [18] that an acetylcholine inhibitor (Physostigmine) improves working memory is exceptionally important. In an accompanying "Perspectives," Robbins, Mehta, and

Sahakian [19] note that "these studies raise the exciting possibility that aspects of working memory may be improved by drugs with selective actions on different neurotransmitter systems, resulting in possible therapeutic benefits for patients with cognitive disorders such as Alzheimer's disease." In addition to valuable therapeutic applications, however, this research advances our understanding of the role of toxins in such costly behavioral problems as Attention Deficit Disorder (ADD), hyperactivity (ADHD), and violent crime.

The neurotransmitter systems discussed by these authors (both monoamines and cholines) are known to be vulnerable to toxins. Like therapeutic agents that act on different neurotransmitters, moreover, toxins can produce dynamic interactions of unsuspected importance. Studies of choline function indicate that enzymes enhancing cholinergic levels can have paradoxical effects due to the combined effects of toxins acting on cholines or monoamines. As several examples will indicate, it is therefore essential to combine assessments of therapeutic value and toxicity when considering the practical implications of neurochemical discoveries.

Some Behavioral Effects of Ach and Ache

This section does not claim to provide a comprehensive survey of the functions of Acetylcholine and its regulation by the enzyme Acetylcholinesterase. Rather it seeks to introduce the importance of these compounds in behavioral regulation, and hence the importance of integrating toxins that affect in any major way the system of choline functions into research in neurotoxicology.

The regulation of acetylcholine (ACh) has been described as follows: "In contrast to most other small-molecule neurotransmitters, the postsynaptic actions of ACh are not terminated by reuptake, but by a powerful hydrolytic enzyme, acetylcholinesterase (AChE). This enzyme is concentrated at the synaptic cleft, ensuring a rapid decrease in ACh concentration after its release from the presynaptic terminal. AChE has a very high catalytic activity (5000 molecules of ACh per AChE molecule per second) and hydrolyzes ACh into acetate and choline. Cholinergic nerve terminals contain a high-affinity, Na+ dependent transporter that takes up the choline produced by ACh hydrolysis [20]."

This system can be the target of both therapeutic drugs [21] and environmental toxins [22]. Physostigmine, an "anticholinesterase"

whose mechanism resembles AChE, is a medication used as a “muscle stimulant” to treat such conditions as Myasthenia gravis [23]. Although it had been reported even before the latest study that anticholinesterases can enhance attention and counteract dementias of the Alzheimer’s type, [24] such positive effects are not without risks. For example, in treatment of Myasthenia gravis, anticholinesterases are known to have a wide variety of negative side-effects on the heart and circulatory system, digestive system, cognition, or other functions and in extreme cases can cause lethal paralysis (note 15). Moreover, studies in Chile indicate that, under some conditions, AChE can “stimulate the aggregation of Abetal-40 into amyloid fibrils” of a sort found in Alzheimer’s disease [25].

These side effects may be more pronounced after exposure to other toxins that have anticholinergic effects. “Among the many interesting drugs that interact with cholinergic enzymes are the organophosphates. These compounds include mustard gas (a chemical widely used in World War I), numerous insecticides, and Sarin, the agent recently made notorious by a group of Japanese terrorists. Organophosphates can be lethal to humans (and insects) because they inhibit AChE,

causing ACh to accumulate at cholinergic synapses. This build-up of ACh depolarizes the postsynaptic cell and renders it refractory to subsequent ACh release, causing neuromuscular paralysis.” (note. 15)

It follows that toxins, like overdoses of a therapeutic anticholinesterase, can have the paradoxical effect of reducing firing in circuits that are activated by ACh. Although an appropriate dose of anticholinesterase may benefit individuals with a deficit of ACh, [26,27] the same or larger doses could have adverse effects on individuals whose normal or higher levels of ACh lead to a “build-up of ACh” and depolarization of postsynaptic cells. Other factors in brain chemistry also produce divergent responses. For example, one study shows that glutathione, an antioxidant that sequesters heavy metal toxins, is protective against AChE toxicity, especially in Neuro 2a cells [28].

Neurotoxic Interference with Cholinergic Functions: Some Selective Examples

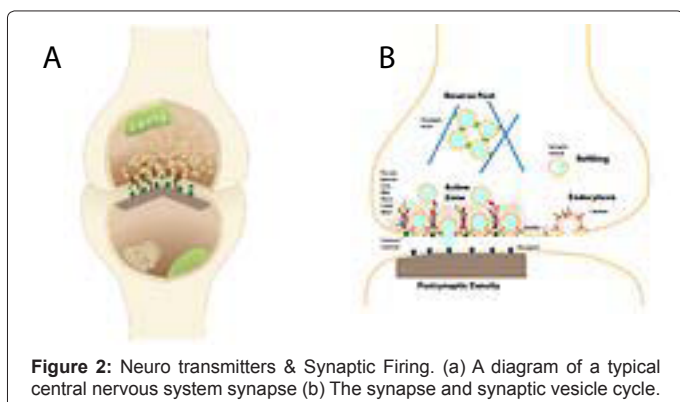
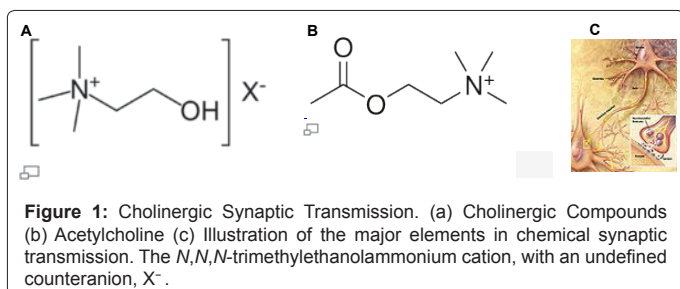
The effects of anticholinesterases can also be modified by toxins that disturb the function of monoamines or catecholamines. The effects of neurotoxicity, especially if arising from biochemical interactions,

Factors	3a: All Violent Crimes	3b: Aggravated Assault	3c: Property Crimes	3d: Welfare Recip/Cap	3e: Median Grade Completed
Population Density (log)	82.42 ^{****} (20.24)	38.77 ^{****} (12.26)	490.91 ^{****} (22.39)	.00574 ^{****} (24.56)	-.08903 ^{****} (-8.23)
Per-Capita Income	-.007 ^{****} (-2.74)	-.0059 ^{****} (-2.81)	NS	NS	.00017 ^{****} (25.23)
Unemployment	NS	2.27 [*] (1.71)	16.05 [*] (1.74)	.00021 ^{**} (2.10)	-.03665 ^{****} (-8.06)
%Black Poverty	40.06 ^{**} (2.33)	27.62 ^{**} (2.07)	NS	NS	-.13322 ^{***} (-2.88)
%Hispanic Poverty	62.11 ^{***} (2.79)	41.23 ^{**} (2.39)	541.5 ^{****} (4.52)	NS	NS
Police/Capita	153423 ^{****} (16.56)	89318 ^{****} (12.42)	821385 ^{****} (16.47)	4.97007 ^{****} (9.34)	NS
Infant Death Rate	1.813 ^{***} (2.78)	1.173 ^{**} (2.32)	NS	.000065 [*] (1.74)	NS
%Housing pre-1950	-526.75 ^{****} (-13.43)	-447.34 ^{****} (-14.69)	-3722 ^{****} (-17.63)	.007379 ^{****} (3.28)	.93843 ^{****} (9.02)
Public Water/Cap	225.34 ^{****} (4.07)	197.4 ^{****} (4.59)	2618 ^{****} (8.78)	NS	1.00734 ^{****} (6.82)
Median Grade Completed	24.68 ^{***} (3.50)	16.82 ^{***} (3.07)	586.7 ^{****} (15.46)	.001109 ^{**} (2.74)	N/A
Lead Present/ Absent	40.80 ^{****} (4.67)	18.49 [*] (2.73)	134.5 ^{****} (2.86)	.003491 ^{****} (6.95)	NS
Manganese Present/Abs.	58.71 ^{****} (6.68)	39.26 ^{****} (5.75)	155.3 ^{****} (3.28)	.004482 ^{****} (8.88)	.05672 ^{**} (2.40)
Alcohol Death Rate	101.62 ^{****} (11.55)	62.46 ^{****} (9.14)	188.4 ^{***} (3.97)	.001186 ^{**} (2.35)	-.10258 ^{****} (-4.35)
Alcohol * Lead	21.48 ^{**} (2.54)	NS	NS	.001626 ^{***} (3.34)	.05316 ^{**} (2.34)
Alcohol * Manganese	55.40 ^{****} (6.54)	36.79 ^{****} (5.59)	117.6 ^{**} (2.58)	.001578 ^{***} (3.24)	.04051 [*] (1.78)
Lead * Manganese	34.89 ^{****} (4.11)	15.57 ^{**} (2.36)	NS	.003126 ^{****} (6.41)	NS
Alcohol * Lead * Manganese	19.21 ^{**} (2.27)	NS	NS	.001764 ^{***} (3.63)	NS
adj r ²	.369	.259	.467	.369	.415
F	97.45	58.60	145.12	97.17	125.02
DF	17,2783	17,2783	17,2783	17,2783	16,2784
p	.0000	.0000	.0000	.0000	.0000

**** p < .0001 *** p < .005 ** p < .05 * p < .10.

NOTE: Cell entries are unstandardized coefficients (t ratio in parentheses).

Table 3: Multiple Regression Model for 50 States [16].



may therefore be of unexpected importance in cognitive and behavioral dysfunctions whose probable causes are slowly becoming apparent [29]. In the last few years, therapeutic treatment of hyperactive or learning disabled children has increasingly relied on agents that regulate neurotransmitter dysfunction. Millions of children diagnosed with ADHD are now routinely treated with Ritalin, which functions (like cocaine) as an excitatory agent for the dopaminergic systems of the basal ganglia which regulate inhibition. Dr. Sydney Walker reports that he has successfully treated many hyperactive children who suffered from excessive burdens of lead or other toxins by detoxification [30]. Where lead or other heavy metals have been identified as abnormally high, others including Dr. William Walsh of the Pfeiffer Treatment Center [31] and Jane Hersey of the Feingold Association, [32] also find that chelation and diet can often reduce hyperactive symptoms without the use of Ritalin [33].

Some generally unknown effects of anticholinesterases provide further evidence that the effects of neurotoxicity on learning and behavior urgently need more attention and research. In a study by Westendorf [34], sodium fluoride (NaF) was found to increase red blood cell permeability and silicofluorides such as $MgSiF_6$ were found to function as anticholinesterases. Two silicofluorides fluosilicic acid and sodium silicofluoride (H_2SiF_6 & Na_2SiF_6) are used in the treatment of public water supplies delivered to over 45% of the U.S. population even though their health and behavioral effects are unknown to the EPA and other governmental agencies [35].

Toxic & Behavioral Effects of Silicofluorides

In addition to biochemical effects of silicofluorides on enzymatic function in the kidney and liver, [36] some fluoride compounds appear to enhance uptake of lead [37]. Exploratory studies using children's blood lead surveys in the states of Massachusetts, New York, and Washington as well as the national sample in NHANES III (total $n > 400,000$) show that in communities using these silicofluorides, uptake of lead from such environmental sources as old housing or industrial

pollution is significantly enhanced compared to communities that do not fluoridate or use sodium fluoride [38-40]. While there are plausible reasons for the enhanced transport of lead among children exposed to silicofluoride-treated water, Westendorf's finding [34] that silicofluorides can function as anticholinesterases also suggests there may be an additional behavioral problem. At the concentration found in water supplies, do silicofluorides act as a muscle stimulant that exacerbates problems of behavioral inhibition (contributing to ADHD) or impairs working memory (contributing to ADD) for many children?

While reliable epidemiological data on ADHD or ADD are not available, geographical data are consistent with the hypothesis that behavioral dysfunctions related to lead, manganese, and other toxic chemicals significantly higher in communities using silicofluorides in water treatment than in those not using these chemicals [38]. To explore this hypothesis further, county-level statistics from the U.S. Census Bureau, CDC, FBI, and EPA were combined and subjected to the same multiple regression analysis previously used to see whether lead or manganese pollution are associated with higher rates of violent crime. Controlling for such pollution and nine socio-economic or demographic variables, the proportion of the population exposed to silicofluorides was a significant predictor of violent crime rates in all U.S. counties with data for 1985, 1991, and 1995 and a predictor of rates of murder and drunkenness for 1995. These findings probably concern behaviors due to poor impulse control or cognitive deficits rather than overall hostility to rules, since there is not a significant association between silicofluoride usage and 1995 county rates of Property Crime (which is usually thought to entail more planning than violence) as well as arrest for possession of either marijuana or heroin/cocaine (both of which probably include arrests of drug dealers and not merely impulsive users). Moreover, the previously noted independent effect of lead pollution on violent crimes (Table 3) was no longer significant once silicofluoride use was added to the equations.

Conclusion

Introducing neurotoxicology to behavioral research and public policy analysis

Although epidemiological data correlating neurotoxins to behavioral dysfunctions do not in themselves demonstrate a causal relationship, they reinforce the need for laboratory studies of the interactions between toxins and neurotransmitter systems. From this perspective, studies like those of Furey may be the first step to more effective approaches to pressing issues of public policy as well as to individual cognitive functioning. Although Physostigmine can be a valuable muscular stimulant in cases of Myasthenia gravis, excessive levels of an anticholinesterase can paralyze nerve function and seriously harm a patient as well as some of those with normal levels of ACh. Similarly, the positive effects of anticholinesterase on the working memory of Alzheimer's patients may be counterbalanced, for others exposed to toxins or with higher baseline ACh levels, by increased motor behavior and impulsivity or by reduced perceptive encoding efficiency and weaker working memory.

Could chemicals with such enzymatic effects combine with other toxins to help explain the veritable epidemic of ADHD and ADD in our nation's children or the increased incidence of Alzheimer's Disease? [41,42] While the paradigm of "one germ, one medicine per disease" has been widely successful for infectious illnesses, the complexity of brain biochemistry, learning and behavior needs a different approach emphasizing the diverse effects of combinations of toxins and chemicals. Given the increasing knowledge of neurotransmitter function and

biochemistry as they relate to behavior and learning disabilities, while further research on the chemical interactions studied in contemporary neuroscience deserves the highest priority, findings to date urgently need to be integrated in the policy-making process. Above all, the education and behavior of our children depends on answering this challenge.

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