

Binding of aluminium ions by *Staphylococcus aureus* 893.

Bradley TJ, Parker MS.

Experientia. 1968 Nov 15;24(11):1175-6.

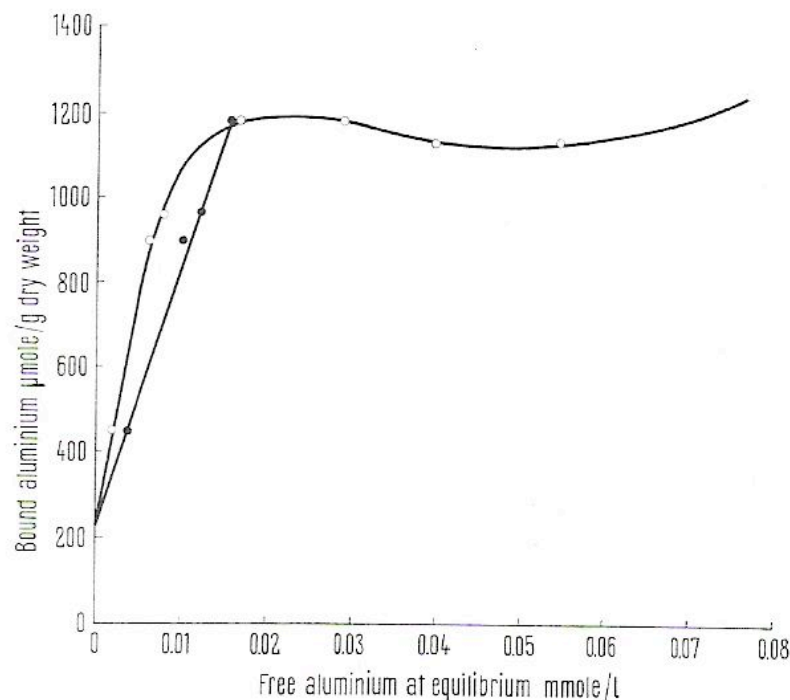


Fig. 1. ○—○ Adsorption isotherm of aluminium by *S. aureus* 893 at 20°C and pH 6.0. ●—● Desorption isotherm of aluminium by *S. aureus* 893 at 20°C and pH 3.0.

Binding of Aluminium Ions by *Staphylococcus aureus* 893

The kinetics of aluminium ion binding from aqueous solution by *Staphylococcus aureus* strain 893 (a wound isolate, University of Strathclyde) have been shown to be rapid, a surface phenomenon and dependant on the hydrogen ion concentration of the solution¹.

The nature of this binding has now been investigated in the pH range 2.0–6.0. 2 mechanisms of binding have been found.

Experimental procedures. Nutrient agar cultures of *S. aureus* 893 were grown as previously described¹. Washed cells were suspended in distilled water ($D_{600\text{nm}}$ of $1.0 \pm 354 \mu\text{g/ml}$ dry weight at 105°C) and used to prepare isolated cell walls (SALTON²).

The uptake of aluminium by cells from solutions containing 10–20 mg/l at pH values from 2.0–6.0 were determined by the method of GILES and MCKAY³. Solution concentrations of aluminium were determined by JONES and THURMAN⁴ method.

The binding of hydrogen ion by cell walls was determined by the method of KENCHINGTON⁵ in 0.05M KCl suspensions with 0.02N HCl using a Radiometer TTTic pH meter and recording unit as described by A. D. BROWN⁶.

Results and discussion. The adsorption isotherm (20°C, pH 6.0) of aluminium ions by cells of *S. aureus* 893 is shown in Figure 1 where 1180 $\mu\text{moles/g}$ dry weight is bound.

The influence of hydrogen ion concentration on the binding of aluminium is shown in the Table where maximum values are stated. The pH shift to more acid values show the association of aluminium ions with acid groups on the cell. At pH values of 4.0–4.4 the amount of aluminium bound has fallen to 240 $\mu\text{moles/g}$, and at pH value of 3.9 and below no detectable binding of aluminium could be determined. Also no significant fall in the pH of the solution was noticed at pH values below 4.0 indicating no hydrogen ion-aluminium ion exchange.

The most abundant aluminium ion in solutions of low concentrations of aluminium at pH values about 4.0 is the mononucleate hydroxide $[\text{Al}(\text{OH})_2]^{+}$, and aluminium is attached as this ionic species to the mobile layer of counter ions associated with the dissociable groups of the staphylococcal cell surface⁷.

With rising hydrogen ion concentration of the medium 3 factors operate to effectively reduce the adsorption of aluminium by the cells. (1) More cations competing for the exchangeable sites on the cell surface; (2) the increase in the electropositivity of the hydrated aluminium ions $[\text{Al}(\text{OH})_2]^{+} \rightarrow [\text{Al}(\text{OH})]^{++} \rightarrow [\text{Al}]^{3+} + \text{H}_2\text{O}$; (3) the number of dissociable groups on the cell surface is reduced.

Competitive binding of aluminium ions by *S. aureus* 893 cells at increasing concentrations of hydrogen ion

pH of Al solutions	Initial pH of <i>S. aureus</i> 893 + aluminium, mixture	pH of reaction mixture at equilibrium	pH of Al mixture	Aluminium bound $\mu\text{moles/g}$
4.35	6.00	5.40	0.60	1180
4.35	4.55	4.50	0.05	240
3.80	3.92	3.90	0.02	nil, or too low to be determined

The desorption isotherm for bound aluminium from *S. aureus* 893 (20°C pH 3.0) is a straight line relationship, indicating the replacement of an $[\text{Al}(\text{OH})_2]^{+}$ ion by a H^{+} . Extrapolation of this line to zero concentration of free aluminium ions yields an intercept of 220 μmoles bound aluminium/g dry weight. This residual aluminium (which corresponds to the amount of aluminium adsorbed from

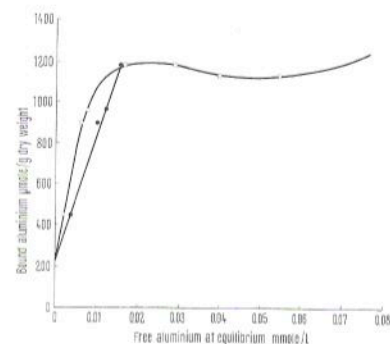


Fig. 1. ○—○ Adsorption isotherm of aluminium by *S. aureus* 893 at 20°C and pH 6.0. ●—● Desorption isotherm of aluminium by *S. aureus* 893 at 20°C and pH 3.0.

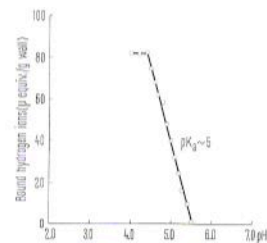


Fig. 2. Hydrogen ion binding of isolated walls of *S. aureus* 893.

¹ T. J. BRADLEY, F. FISH and M. S. PARKER, *J. Pharm. Pharmacol.* 17, 98S (1965).

² M. R. J. SALTON, in *The Bacterial Cell Wall* (Elsevier Publishing Co., New York 1964).

³ C. H. GILES and R. B. MCKAY, *J. Bact.* 89, 390 (1965).

⁴ L. H. JONES and D. A. THURMAN, *Pl. Soil* 9, 131 (1958).

⁵ A. W. KENCHINGTON, in *Analytical Methods of Protein Chemistry* (Pergamon Press, London 1960), vol. 2.

⁶ A. D. BROWN, *J. molec. Biol.* 12, 491 (1965).

⁷ J. N. BUTLER, in *Ionic Equilibria: A Mathematical Approach* (Addison-Wesley, Reading, Massachusetts 1964).

⁸ J. P. HUNT, in *Metal Ions in Aqueous Solution* (W. A. Benjamin, New York 1963).

⁹ F. GALDIERO, M. LENBO and M. A. TUFANO, *Experientia* 24, 34 (1968).

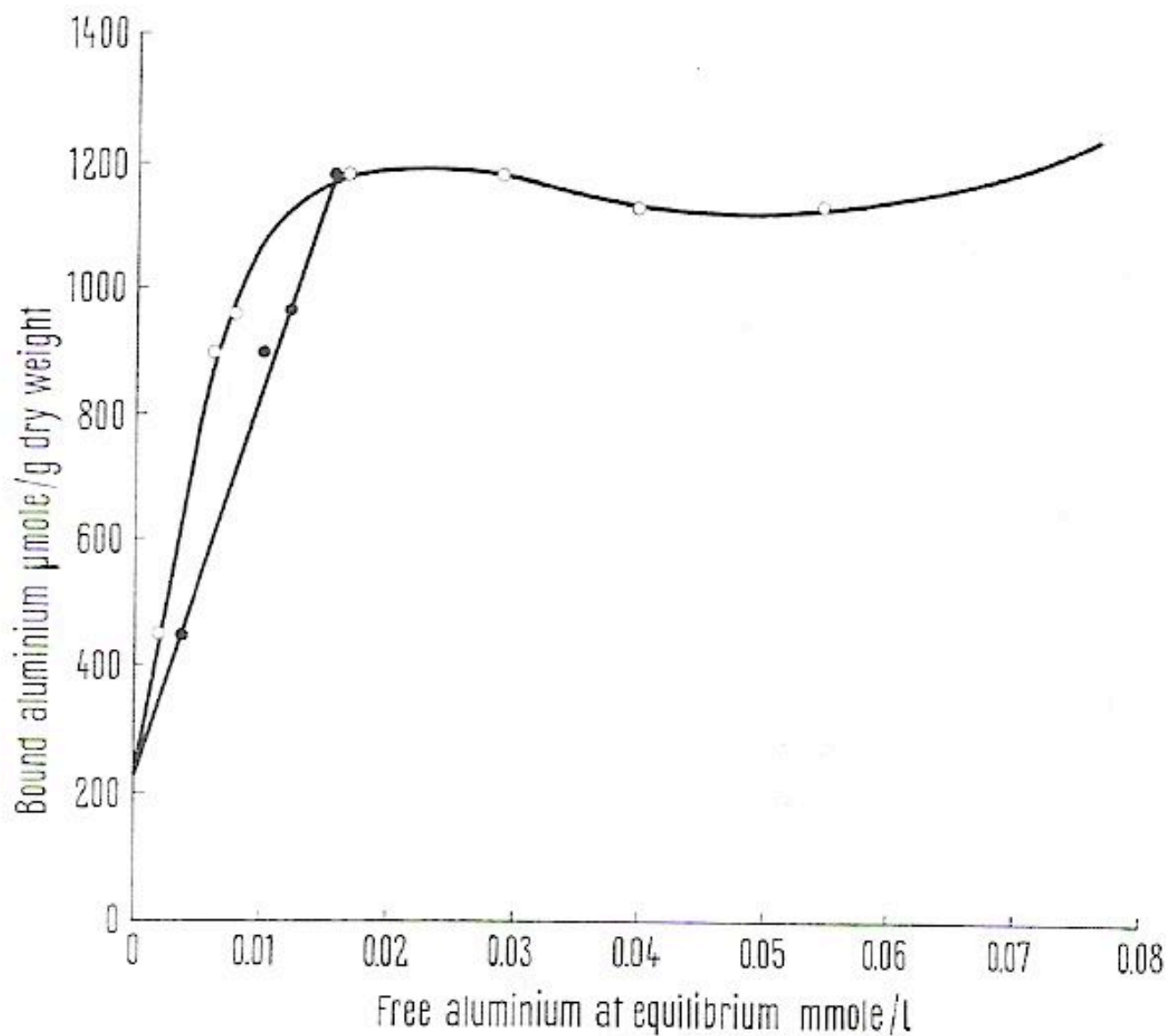
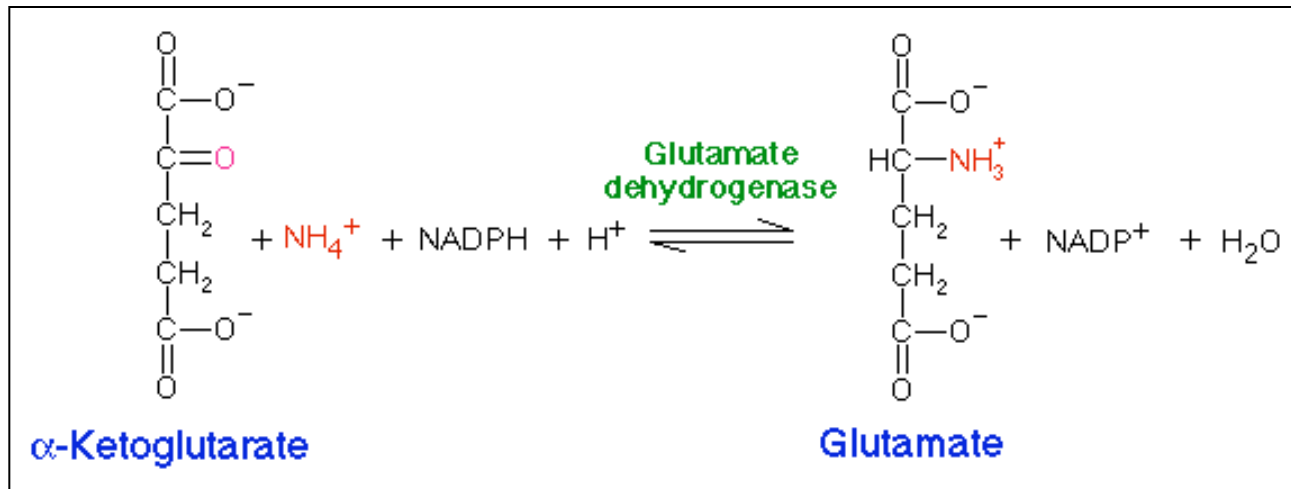


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Consequences of aluminum accumulation

Aluminum interferes with glutamate dehydrogenase



Effect of long-term aluminum feeding on kinetics attributes of tissue cholinesterases

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Elevated levels of Al in autopsied brain samples of patients with certain neurological disorders, such as Parkinsonism [19], amyotrophic lateral sclerosis [41], or senile dementia of Alzheimer type (SDAT) [40], have been reported. Neurotoxic effects of Al and its role in Al-induced encephalopathy, such as dialysis encephalopathy, have been described [20]. The administration of Al compounds causes neuroanatomical and neurochemical alterations in the brain: neurofilament accumulation [48] followed by nerve cell loss [21], and a suppressing influence on the cholinergic system [58] are among the cholinotoxic effects of this metal, and these are similar to those seen in SDAT [20].

Al is considered a potential etiologic factor in Alzheimer's disease (AD) [12,18]. Neurotoxicity from excess brain exposure to Al is well documented from both clinical observations and animal experiments [9,12,36]. Long-term administration of soluble salts of Al to rats can result in a neuropathological condition in which selective neuronal loss and impairment of cholinergic functions are evident [5]. High density of senile plaques in selected brain regions is a characteristic feature of AD [45], and Al is believed to represent a key element for plaque formation [56]. Conformational changes in amyloid peptide in the presence of added Al has been demonstrated *in vitro* [1,22]. Recently, it has been shown that enhancement of inflammation and interference with the function of cholinergic projections may represent the modes of action through which Al may cause learning and memory deficits and contribute to pathological processes in AD [43].

There is some evidence of neurochemical alterations induced in the cholinergic system of several rodent species by Al *in vivo* [20]. We have reported the effect of long-term Al feeding on oxidative energy metabolism in rat liver, brain and heart mitochondria [52]. The toxic effects of Al on different membrane systems have been evaluated [51]. Our own studies have shown that the phospholipid compositions of rat brain synaptic plasma membranes, microsomes and myelin, as well as Na⁺, K⁺ ATPase kinetics, were significantly altered after long-term Al feeding [37,38].

Consequences of aluminum accumulation

Aluminum inhibits the activity of acetylcholinesterase

Acetylcholinesterase Inhibition and Neurological Inflammation

Aluminum	Alzheimers
Organophosphates	Parkinson's
Pyridostigmine	ALS/Gulf War Syndrome
Aluminum	Autism
Tetanus Toxin	

Acetylcholinesterase Inhibition

Muscarinic Stimulation

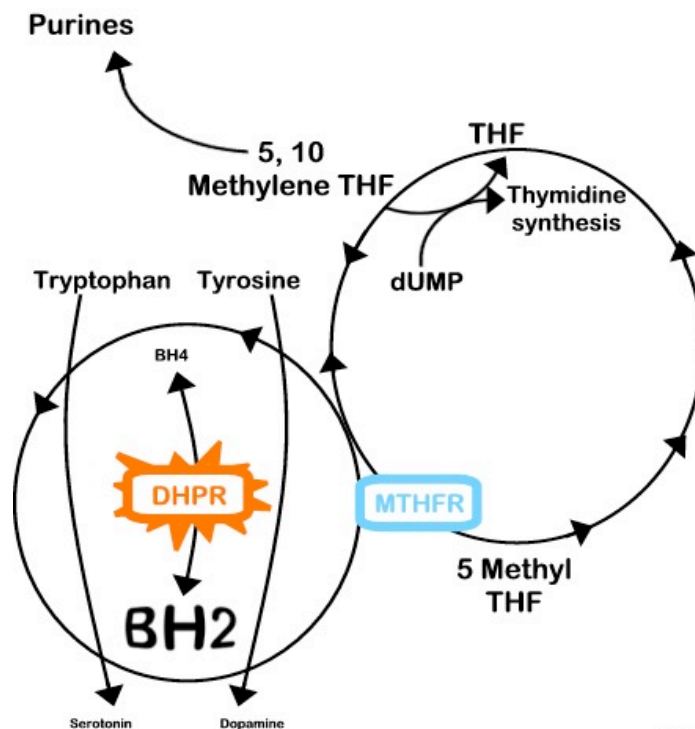
- Pinpoint pupils
- Blurred vision
- Hypersecretion
- Bladder incontinence

Nicotinic Stimulation

- Muscle twitching
- Muscle weakness
- Dilated pupils

Consequences of aluminum accumulation

Aluminum inhibits the activity of DHPR resulting in decreased BH4



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Altindag ZZ, Baydar T, Engin AB, Sahin G.

Effects of the metals on dihydropteridine reductase activity.

Metals are the oldest toxins known to human. Particularly, occupational and environmental exposure to aluminium, lead, mercury, cadmium, and manganese cause serious health problems by interaction with biological systems. Cellular targets of these metals are mostly specific biochemical processes (enzymes) and/or membranes of cells and organelles. To prevent and/or reduce the untoward or irreversible toxic effects of the metals by using biomarkers are as important as to know and to understand of their toxicity mechanisms. Dihydropteridine reductase (DHPR), which possessed essential thiol groups at the activity site, plays a crucial role in the maintenance of tetrahydrobiopterin (BH₄). BH₄ is the cofactor in the synthesis and regulation of neurotransmitters. A limited number of the evidences have shown that DHPR may be a target for the metals. Therefore, the present study was designed to assess possible in vitro effects of the commonly exposed metals on the enzyme activity. It was found that aluminium, cadmium, mercury, di-phenyl mercury, lead, diethyl lead, in chloride forms, and manganese, in sulphate form, led to statistically significant decreases in DHPR activity, in a concentration-dependent manner, in vitro.

Serum aluminum levels and erythrocyte dihydropteridine reductase activity in patients on hemodialysis.

Aluminum intoxication due to aluminum-containing antacids or dialysate can cause encephalopathy in patients undergoing hemodialysis, but the biochemical mechanism has not been defined. The enzyme dihydropteridine reductase (DHPR) is essential for the maintenance of normal brain concentrations of tetrahydrobiopterin, which is itself required for the synthesis of specific neurotransmitters. This enzyme is also present in erythrocytes. We measured erythrocyte DHPR activity and concentrations of the biopterin derivatives of its substrate and of aluminum in 38 patients on hemodialysis who had no clinical evidence of encephalopathy. Serum aluminum levels ranged from 15 to 190 micrograms per liter (mean, 67.6 +/- 7.7) as compared with 4.9 +/- 0.99 micrograms per liter in normal subjects. DHPR activity was inversely related to the serum aluminum concentration ($r = -0.61$, P less than 0.001) and was less than the activity predicted from the hemoglobin concentration in these patients. Serum concentrations of biopterin derivatives were markedly elevated. Eighteen patients were given the aluminum-chelating agent deferoxamine in a single dose, after which DHPR activity doubled. These studies suggest that aluminum inhibits DHPR activity in erythrocytes and that aluminum chelation reverses this effect. Although we did not directly measure DHPR activity in the brains of dialysis patients without encephalopathy, we propose that the reduction in activity in erythrocytes may reflect a similar reduction in the brain. Our findings could help to explain the encephalopathy associated with aluminum intoxication.

Brain Res. 2002 May 10;935(1-2):47-58

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Preferential resistance of dopaminergic neurons to the toxicity of glutathione depletion is independent of cellular glutathione peroxidase and is mediated by tetrahydrobiopterin.

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Depletion of glutathione in the substantia nigra is one of the earliest changes observed in Parkinson's disease (PD) and could initiate dopaminergic neuronal degeneration. Nevertheless, experimental glutathione depletion does not result in preferential toxicity to dopaminergic neurons either in vivo or in vitro. Moreover, dopaminergic neurons in culture are preferentially resistant to the toxicity of glutathione depletion, possibly owing to differences in cellular glutathione peroxidase (GPx1) function. However, mesencephalic cultures from GPx1-knockout and wild-type mice were equally susceptible to the toxicity of glutathione depletion, indicating that glutathione also has GPx1-independent functions in neuronal survival. In addition, dopaminergic neurons were more resistant to the toxicity of both glutathione depletion and treatment with peroxides than nondopaminergic neurons regardless of their GPx1 status. To explain this enhanced antioxidant capacity, we hypothesized that tetrahydrobiopterin (BH(4)) may function as an antioxidant in dopaminergic neurons. In agreement, **inhibition of BH(4) synthesis increased the susceptibility of dopaminergic neurons to the toxicity of glutathione depletion, whereas increasing BH(4) levels completely protected nondopaminergic neurons against it. Our results suggest that BH(4) functions as a complementary antioxidant to the glutathione/glutathione peroxidase system and that changes in BH(4) levels may contribute to the pathogenesis of PD.**

Consequences of aluminum accumulation

**Aluminum leads to stimulation
of the
immune system**