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Toxicity and the cardiovascular activity of organotin compounds: a review

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A comprehensive review on toxicity of organotin compounds including sources of their intake and mode of action, and cardiovascular activity of organotin compounds is presented. Further research to develop novel useful organotin compounds having hypertensive activity needs to be carried out. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: organotin compounds; cardiovascular activity; toxicity; sources of human exposure; mode of action

Introduction

Organotins, important environmental pollutants, belong to the most widely used organometallic compounds for agricultural, industrial and biomedicinal applications, with an estimated annual production of approximately 60 000 tons, and some of them are potential candidates for cancer chemotherapy. The chemistry of organotin compounds has grown enormously in the last four decades as one of the strongest areas in the interdisciplinary organometallic field owing to tremendous significance of organotins.[1–4] Since then, organotins have been used in diversified commercial applications such as polyvinyl chloride (PVC) stabilizers, industrial biocides, industrial catalysts, surface disinfectants including hospital and veterinary disinfectants, surface-modifying and curing agents,[1–4] bacteriostats, antimicrobials and slimicides, laundry sanitizers and mildewcides, rodent-repellents,[1,3,4] scintillation detectors for γ- and X-rays,[4] ballistic additives for solid-rocket engine fuels[4] and ionophores in liquid membrane ion-selective electrodes.[5,6]

Diorganotin compounds, particularly di-*n*-butyltin (DBT), diphenyltin (DPhT) and di-*n*-octyltin (DOT) compounds, are the most effective heat/sunlight stabilizers for PVC plastics (in rigid PVC pipes, panels and soft wall-coverings, furnishings, floorings, toys and PVC containers for food), and are used as catalysts for the production of microcellular, light-stable elastomeric, flexible or semiflexible polyurethane moldings[7] and for the curing of room-temperature vulcanized (RTV) silicone elastomers to produce flexible silicone rubber.[3] Triorganotin compounds, including tri-*n*-butyltin (TBT), tri-cyclohexyltin (TCT) and triphenyltin (TPhT) compounds, are used in agriculture as fungicides, anti-helminthics, miticides, herbicides, nematocides, ovicides, molluscicides, acaricides and pesticides, and in industry as biocides, and were used as marine anti-fouling agents in paints for large ships.[1,2,8–10] A recent review[11] presented the biological implications of organotin compounds as biocides in marine anti-fouling coatings. In addition to the major use of tri-*n*-butyltin compounds in anti-fouling paints, they are also used as anti-fungal agents in some consumer products, including certain PVC (vinyl) floorings.[12]

Along with these numerous applications, and with the rapid growth in the production and consumption of organotin compounds, the concern about possible environmental and health effects increased. Because of their wide applications, several studies have focused on the increasing amounts of both organic and inorganic tin present in the environment, having been evaluated as the third most important elemental pollutant in the ecosystem. This has naturally raised the concern that tin may enter and accumulate in the environment,[13,14] and therefore, the human food chain.[15] Much of the research describing the environmental distribution of organotin compounds has, understandably, focused on the spread of TBT and its break-down products (including DBT) in the marine environment. The relative persistence of butyltins, combined with their affinity for biological tissues, has led to their widespread occurrence in fish, snails, mussels, seals and dolphins.[16,17] In higher species, including mammals, organotin compounds tend to accumulate in certain organs, namely the liver, kidneys and brain.[18] However, some triorganotin compounds, viz. Brestan® (triphenyltin acetate), Duter® (triphenyltin hydroxide) and Plictran® (tricyclohexyltin hydroxide), are commercially used as fungicides and acaricides, respectively. The organotin compounds have the advantage over the very effective mercury compounds of being degraded to relatively harmless inorganic tin compounds. Although their use is decreasing, since their biodegradation is very slow, organotin compounds are very persistent in the environment, thus causing toxicological problems to humans and animals,[2,15,19] and induce imposex (imposition of male sex characters onto the female) in several marine species[20,21] as well as neurotoxic[22–25] and immunotoxic effects[26–28] in higher animals. Therefore, a few recent studies[29,30] have concentrated on the importance of biodegradation of organotin compounds, particularly triorganotin compounds, using biological thiols[29] and marine bacteria,[30] since triorganotin compounds might have been accumulated in marine ecosystems owing to their extensive use as marine anti-fouling agents.

Many *in vitro* studies have been performed in order to explain the mechanism that is responsible for the toxicity of organotin compounds in whole organisms. In addition to their neurotoxic effects, organotin compounds have also been shown to interfere with heme metabolism as well as the cardiovascular system.[31] However, despite the concern that

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has been raised about the environmental and health effects caused by organotin compounds, an area which has raised the chemistry of organotin compounds to new horizons is their potential application in metal-based chemotherapy as metallopharmaceuticals exhibiting anti-tumor,[32–41] anti-microbial,[42–46] anti-tuberculosis,[47] anti-inflammatory[48–54] and trypanocidal[55] activities. This prompted researchers to focus attention on the speciation of organotin compounds in biological systems, which has revealed that the biological activity of these compounds may be due to the presence of easily hydrolyzable groups (easily dissociable chelating ligands) yielding intermediates such as $R_nSn^{(4-n)+}$ ($n = 2$ or 3) moieties, which may bind with DNA and proteins.[32] Therefore, more emphasis should be given to considering the toxic effects of organotin compounds along with sources of human exposure to them before describing their biological activity. In view of this, a comprehensive review covering details of toxic effects and mode of action of various organotin compounds along with the possible sources of their intake in human beings, and cardiovascular activity of organotin compounds, in particular, is presented herein.

Sources of Animal/Human Exposure to Organotin Compounds

The gastrointestinal tract is a major route by which humans are exposed to environmental chemicals. The major sources of organotin compounds intake for humans are dietary sources, such as seafood and shellfish,[56,57] food crops,[58] and drinking water which are contaminated because of the exposure to antifouling agents and fungicides, and because of the leaching from PVC water pipes and PVC plastics used for packaging of food items,[59] respectively. Other possible routes of human exposure to organotins include their use as anti-fungal agents in wood treatment, industrial water systems and textiles. It has been recognized[59] that organotins used in various consumer products can migrate from such products during normal use and contribute their widespread presence in dusts from the indoor environment. Therefore, additional sources are indoor dusts, textiles and liquids stored in plastic containers, including various alcoholic beverages (port, red and white wines).[60,61] Moreover, the global use of TBT anti-fouling paints has resulted in contamination on a global scale with devastating impacts on populations of oysters and other marine molluscs.

Measured exposure levels of organotin compounds, such as di-*n*-butyltin and tri-*n*-butyltin compounds, in wildlife and human tissue samples[62,63] are in the range of 3.0–100.0 nM. Takahashi[62] reported the presence of butyltin residues in the livers of monkeys and other mammals as well as human livers, and suggested that uses in consumer products may represent an important route. It has been reported that in higher species, including mammals, organotin compounds tend to accumulate in certain organs, namely liver, kidney, and brain.[18] Organotins efficiently penetrate through the skin and easily cross the placenta and blood–brain barrier.[64,65]

Toxicity

Organotins are known to be toxic at relatively low levels of exposure, not only to marine invertebrates but also for mammals and other animals. The toxicity of the organotin compounds increases with the number of alkyl groups attached. The most toxic organotin compounds are the trialkyltin compounds, followed by the dialkyl- and monoalkyl-tin compounds, with the ethyl derivative in each group being reported as the most toxic.[4] Of the triorganotin compounds, triphenyltin compounds are moderately toxic, but less toxic than trialkyltin compounds with shorter alkyl chains, such as trimethyltin (TMT) compounds.[4] Organotin compounds are irritating to eyes, respiratory tract and skin, and some can cause cerebral edema and produce central nervous system and cardiovascular effects. Manifestations of toxicity are due principally to effects on the central nervous system: headache, nausea, vomiting and dizziness, and sometimes convulsions and loss of consciousness. Photophobia, epileptic seizures and mental disturbances can occur. Epigastric pain is reported, even in poisoning by inhalation.

Comparison of the effects of various trialkyltin compounds indicated that the compounds with short alkyl groups, such as trimehtyltin (TMTC) and triethyltin (TETC) chlorides, were mainly neurotoxic, causing neuronal degradation, cerebral edema[28] and depleted adrenal epinephrine in rats,[66] whereas organotin compounds with alkyl chains of intermediate length [tri-*n*-propyltin (TPTC) and tri-*n*-butyltin (TBTC) chlorides] and triphenyltin chloride (TPhTC) were mainly immunotoxic[28] causing a dose-related reduction of thymus weight, and the higher homologs [tri-*n*-hexyltin (THTC) and tri-*n*-octyltin (TOTC) chlorides] were only slightly toxic or not toxic at all. The more lipophilic compounds, TPTC, TBTC, THTC and TPhTC, were most toxic in reducing thymidine incorporation at very low concentration (0.05–1.0 μM) and cytotoxic to thymocytes.[67] Triphenyltin acetate was cytotoxic to mouse thymocytes *in vitro*.[68] Further, TET and TPhT compounds induced muscle contracture in mouse diaphragm while TBT had comparatively less potency and efficacy in inducing muscle contracture.[69,70] Both TET and TPhT compounds had detrimental effect on growth and development of rats and guinea pigs at dietary levels of 5–50 ppm.[71,72]

The toxic action of triethyltin compounds (powerful metabolic inhibitors) on the central nervous system of rodents was first described by Stoner *et al*.[73] Later on Magee *et al*. reported that 20 mg (triethyltin)/kg feed induced interstitial edema of the white matter of brain and spinal cord without nervous damage with lesser changes in peripheral nervous system.[74] The concentrations of neurotransmitters such as norpinephrine, serotonin and dopamine in adult rat brain have also been reduced.[75] The higher trialkyltin homologs, such as tricyclohexyltin (TCT) and trioctyltin (TOT) compounds, were found to be only toxic; however, further metabolism *in vivo* converted them to their dialkyltin forms, which are also highly immunotoxic.[26,27] Organotins are probably absorbed to a limited extent by skin and gastrointestinal tract, and they easily cross the placenta and blood–brain barrier.[64,65,76] Elevation of blood sugar, sufficient to cause glycosuria, has occurred in some cases.[77] The phenyltin fungicides, such as Super Tin®/Duter® and Brestan®, are less toxic than ethyltin compounds, which have caused cerebral edema, neurological damage and death in severely poisoned individuals who were exposed dermally to a medicinal compound of this type. No deaths and very few poisonings have been reported as a result of occupational exposures to phenyltin compounds.[78] Heart failure is seen in rats given a lethal oral dose of triphenyltin acetate (TPhTA) along with severe congestion and hemorrhages of the lungs.[79] Upper respiratory tract irritation and shortness of breadth have also been reported in human inhalation cases. Hemolysis is

caused by TPhTC at low concentrations in animal blood, but not in human blood.[80]

A single oral dose of DOT, DBT and TBT compounds induces a dose-related reduction of the relative thymus weight in rats, and impaired cell-mediated immunity was observed after dietary exposure to TPhT compounds for several weeks.[27,28,81] Low-dose dietary bis(tri-*n*-butyltin)oxide (TBTO) exposure induced atrophy of the thymus and peripheral lymphoid organs, depleted iron stores in spleen and erythrocyte rosettes in mesenteric lymph nodes, decreased activity of the pituitary-thyroid axis, and increased LH immunoreactivity and secretion.[81] Furthermore, reduced birth weight and thymus involution, observed upon exposure of pregnant rats to organotin compounds, can be caused by excessive glucocorticoid levels.[64,65,82] The disruption of 11β-hydroxysteroid dehydrogenase type 2 (11 β-HSD2) function by organotin compounds is responsible for the enhanced glucocorticoid concentrations.[83] The circulating cortisol levels remained elevated throughout adult life, indicating a permanently disturbed regulation of the hypothalamic–pituitary–adrenal axis, which leads to a higher susceptibility for cardiovascular and metabolic disorders including obesity, insulin resistance and typeII diabetes.[84,85]

Mode of Action

Triorganotin compounds affect a variety of biochemical and physiological systems and that their 'apparent mode of action' may vary with the compound and its dose, and the species and route of administration. It has been reported that triorganotin-associated neurotoxicity may be due to an altered calmodulin (CaM) activity in brain because TET (0.5, 1.0 and 1.5 mg/kg/day) and TMT (0.75, 1.50 and 2.50 mg/kg/day) inhibited Ca^{2+}-ATPase in a dose-dependent manner but TBT exhibited its inhibitory effect only at the highest dose (2.50 mg/kg/day) in rat brain *in vivo*.[86] Low concentrations of TPhT and other organotin compounds inhibit the H^+ translocation of the membrane-bound portion of H^+-ATPase and some other ATPases, and ion channels such as the Na^+K^+ and the Ca^{2+} translocating ATPases are also affected.[87] Triphenyltin compounds have been shown to increase the intracellular Ca^{2+} concentration of mouse thymocytes, and the cytotoxicity could be caused by the resultant disruption of homeostasis. A likely cause for the increase in intracellular Ca^{2+} is an inhibition of the sequestering of Ca^{2+} by Ca^{2+} translocating ATPases.[88] Organotins may also react with thiol groups in proteins.[80,89] Triphenyltin chloride inhibits superoxide production by human neutrophils,[87] and the hyperglycemic action of triphenyltin fluoride may be due to the inhibition of insulin release.[90]

The mitochondria are the preferential target for many toxic species; therefore, it has been reported much earlier that mitochondrial oxidative phosphorylation in rat liver is inhibited by trimethyltin and triethyltin compounds,[1,22] and they induce uncoupling of mitochondrial energy transduction and exchange of external Cl^- for intramitochondrial OH^- ions.[22] A review[91] on triorganotin compounds as ionophores and inhibitors of ion translocating ATPases has reported that triorganotins inhibit H^+-ATPase, Na^+K^+-ATPase of cell membranes and the Ca^{2+} translocating ATPase of sarcoplasmic reticulum. It has been reported[92] that trialkyltins (TATs) enter the mitochondria as lipophilic cations using the negative-inside potential of mitochondria as a driving force, and uptake is followed by extrusion as $(alkyl)_3SnOH$ compounds. Therefore, the entry of TATs into the mitochondria induces a collapse of the membrane potential which is responsible for the opening of selective anionic channels which could explain the swelling of mitochondria observed in a chloride medium.[92] It has long been established that triorganotins are anionophores and able to catalyze Cl^-/OH^- exchange; however, TBT is able to inhibit Cl^- and NO_3^- transport via inner membrane anion channel (IMAC)[93] at doses below those required to catalyze rapid rates of Cl^-/OH^- exchange (>0.8 nmol TBT/mg of mitochondrial protein). However, TBT is a potent inhibitor of malonate uniport via IMAC (95% at 0.9 nmol/kg) in F1 F0 ATPase, and the potency of inhibition increases with hydrophobicity in the sequence TMT < TET < TPT < TPhT < TBT, which suggests that the binding site is accessible from lipid bilayer.[93] The most sensitive indices of toxicity[94] of triorganotin compounds, such as TPhTC, TPhTA (Brestan®), TCTH (Plictran®) and TBTO, appeared to be associated with changes in lymphatic tissues and blood composition when given orally to young/adult mice (250/750 µequiv. organotin/kg diet) instead of their toxicity due to cerebral edema, alteration in adrenal epinephrine level, liver nonprotein –SH groups or the activity of digestive enzymes.

Triorganotins are also potent inducers of apoptosis in various cell types and there are two major pathways by which apoptotic cell death occurs: one is trigged by a cytokine mediator and the other is by a mitochondrion-dependent mechanism.[95] At low doses, TBT moiety interacts selectively with critical thiol residues in the adenine nucleotide translocator and opens the permeability transition pore, thereby decreasing mitochondrial membrane potential and releasing cytochrome c from mitochondria, a series of events consistent with established mechanistic models of apoptosis.[95] It has been reported[96] that TBT moiety is a potent activator of extracellular signal-regulated protein kinase (ERK), c-Jun NH(2)-terminal kinase (JNK) and p38 mitogen-activated protein kinases (MAPKs) pathways, and Ca^{2+} mobilized from intracellular stores plays an important role for the phosphorylation of MAPKs in CCRF-CEM human T lymphoblastoid cells. The potentials of MAPKs phosphorylation and of cellular damage were TBTC > DBTC > monobutyltin chloride (MBTC).

Bis(tri-*n*-butyltin) oxide (TBTO) produced dose- and time-dependent decrease in the content and functional activity of intestinal cytochrome P-450, together with an elevation (3-fold) in the activity of microsomal heme oxygenase, and these studies indicated that organotins may alter the cytochrome P-450-dependent metabolism of xenobiotics and natural substrates of this monooxygenase system in the small instestine.[97] Further, five-coordinate organotin compounds influence mitochondrial functions in the same three ways as triorganotin compounds, and unlike triorganotin compounds they inhibit the energy conservation system at much lower concentrations like oligomycin.[98] A review on biological activity of tin and immunity reported[99] that organotins act mainly on cellular immune systems. The mechanism appears to be due to their hydrophobicity-dependent intracellular distribution and their action on phospholipids metablosim, including the inhibition of intracellular phospholipid transport of the Golgi apparatus and the endoplasmic reticulum, and the subsequent inhibition of the membrane-mediated signal transduction system leading to DNA syntheses via phospholipids turnover and Ca^{2+} mobilization.

Cardiovascular Activity of Organotin Compounds

Cardiovascular activity of organotin halides/hydroxides/oxides

Organotins have been reported to interfere with heme metabolism as well as the cardiovascular system.[31] Stoner *et al*.[73] observed vasodilatation in rabbits following mono-, di-, tri- and tetraalkyltin treatment. In acute and chronic experiments, they observed that triethyltin (Et_3Sn) compounds (most toxic) produced muscular weakness followed by some recovery, followed by muscular tremors, convulsions and death. The main site of action of these alkyltin compounds was the central nervous system, and it was unassociated with concentration of tin at any particular site. The experimental studies on the effects of *n*-butyltin salts on hemolysis *in vitro* indicated that the hemolytic action of Bu_3SnCl on red blood cells of rabbits was greater than Bu_2SnCl_2 by a factor of 100, whereas Bu_4Sn scarcely showed any action.[100] In DBT-treated mice (injected intraperitoneally), 2,3-dimercapto-1-propanol (BAL) provided high protection both as a therapeutic and as a preventive measure, whereas in TBT-treated animals, BAL acted to only slightly delay the lethal time.[100]

The pharmacological study on bis(tri-*n*-butyltin) oxide (TBTO) on rats, rabbits and dogs indicated that TBTO caused a fall in blood pressure that resulted from a depression of the vascular smooth muscle.[101] The death of the animal in a sub-chronic study of TBTO was due to respiratory arrest by a central mechanism, but its action on the *ortho*- and *para*-sympathetic system is slight and non-specific. On the other hand, Tauberger observed that intravenous administration of triphenyltin acetate (TPhTA) in cats at a dose of 1 mg/kg produced an increase in blood pressure and a short interruption of respiration, followed by stimulation of respiration and clonic contractions of the limb muscles.[102] The repeated administration of 1–2 mg/kg at 20–60 min intervals led to arterial hypotension. A decrease in the effect of noradrenaline on blood pressure was also reported. Death took place from paralysis of the respiratory centers after the administration of 4–14 mg/kg of TPTA. When TPTA was given orally to groups of young rats, 10 of each gender, at dose levels of 0, 5, 10, 25 and 50 ppm for 12 weeks, a decrease in the number of leukocytes in the blood was reported at 10 ppm and above, and at 50 ppm the hemoglobin was reduced.[103a] At the highest level there was a decrease in the organ : heart ratio for the thyroid, pituitary and pancreas in all animals, and uterus and ovary in the females. Similarly, the oral administration of triphenyltin hydroxide (TPhTH) resulted in a decrease in the number of leukocytes at 25 ppm in females and a decrease of hemoglobin and leukocytes in each sex at 50 ppm.[103a,b] Similar results of decreasing leukocytes as well as erythrocytes and hemoglobin content of the blood, were also observed when TPhTA (5–20 ppm)/TPhTH (5–20 ppm) was given orally to guinea pigs for 12 weeks.[103,104] Also basophilic 'stippling' in erythrocytes was observed. No histopathological details of these studies are yet available.

Tricyclohexyltin hydroxide (Plictran®) has been reported to interact with mammalian heme metabolism,[31] and inhibited[105] *in vitro* both oligomycin-sensitive (o.s.) Mg^{2+}-ATPase and Ca^{2+}-ATPase activities in beef heart mitochondria at nanomolar concentrations [Fig. 1(a)] at pH 7.5. However, Plictran® did not affect the oligomycin-insensitive (o.i.) Mg^{2+}-ATPase activity at any concentration studied.[105] It is well established that mitochondrial membrane contains o.s. Mg^{2+}-ATPase and Ca^{2+}-ATPase, which are involved in the terminal step of oxidative phosphorylation, resulting in the synthesis of ATP[106] and in the maintenance of cytoplasmic Ca^{2+} levels,[107] respectively. The significant inhibition of o.s. Mg^{2+}-ATPase and Ca^{2+}-ATPase suggests that Plictran® may be interfering with oxidative phosphorylation and thereby reducing ATP synthesis and calcium ion transport, respectively, in beef heart mitochondria. Substrate activation kinetics revealed that Plictran® inhibited o.s. Mg^{2+}-ATPase uncompetitively and Ca^{2+}-ATPase non-competitively[105] [Fig. 1(b)].

Triorganotin compounds such as Ph_3SnCl, $Ph_3Sn(OAc)$ (Brestan®) and Cy_3SnOH (Plictran®) (the most potent), altered[94]

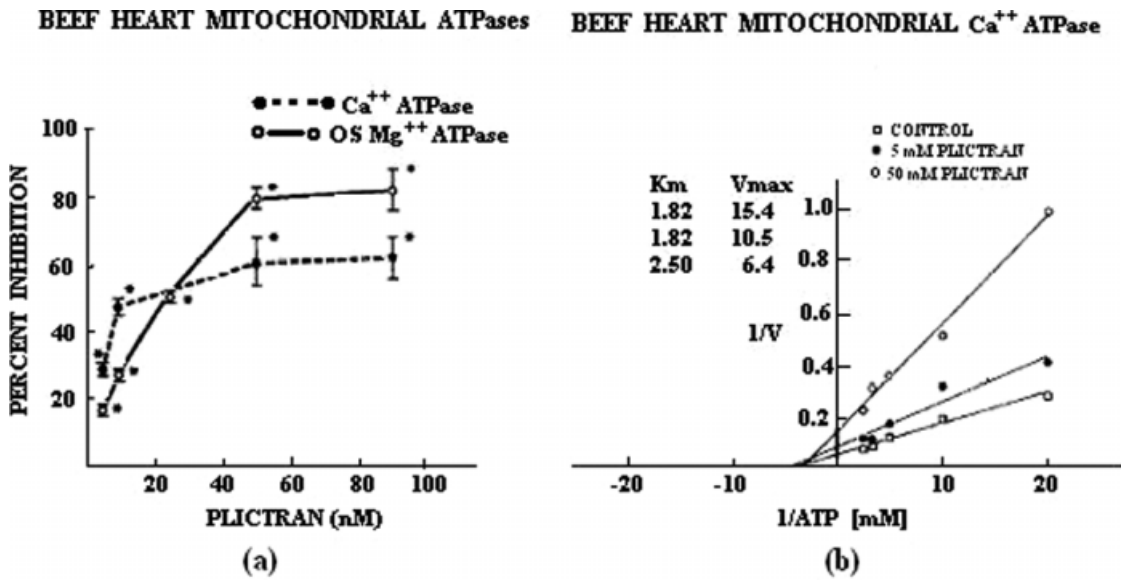


Figure 1. (a) Percentage inhibition of beef heart mitochondrial Ca^{2+}-ATPase (●---●) and oligomycin-sensitive Mg^{2+}-ATPase (○---○) activities by Plictran. * Significant difference ($p < 0.05$) between absence and presence of Plictran in reaction; (b) effect of Plictran on ATP activation kinetics of Ca^{2+}-ATPase in beef heart mitochondria. ATP concentration was varied as shown from 0.5–4 mM, all other conditions remaining constant. Control, (□---□), 5 nM Plictran (●---●), 50 nM Plictran (○---○). Each point in the graphs represents mean ± SE of three different preparations, each assayed in triplicate.[105].

Table 1. Effects of dietary organotins on body, heart and spleen weights and blood composition of male mice

Organotin compound	Dietary level μequiv./ kg	Weight relative to control (%)[a]		Spleen weight relative to control (%)[b,c]	Blood composition relative to control (%)[b,d]			
		Body	Heart		Hb[e]	Hec[f]	Erythrocytes	Leucocytes
Ph_3SnCl	78	99 ± 3	104 ± 4	88	112	107	106	98
	260	86 ± 2	97 ± 13	63	108	100	104	69
	780	69 ± 2	63 ± 5	61	118	113	113	66
$Ph_3Sn(OAc)$	78	–	–	73	100	99	–	72
	260	64 ± 3	67 ± 4	63	104	102	–	67
	780	–	–	51	115	109	110	66
Cy_3SnOH	78	–	–	110	105	103	102	108
	260	76 ± 2	79 ± 4	91	105	108	104	90
	780	–	–	58	116	113	107	82
$(Bu_3Sn)_2O$	260	72 ± 2	82 ± 3	–	–	–	–	–
	780	–	–	86	104	101	102	106
	2340	–	–	63	98	94	96	69
$[(PhCMe_2CH_2)_3Sn]_2O$	260	101 ± 3	93 ± 5	–	–	–	–	–
	780	–	–	80	100	102	100	89
	2340	–	–	73	122	119	109	81
$PhSnCl_3$	780	91 ± 3	92 ± 5	–	–	–	–	–
	2340	–	–	122	97	98	96	91
Ph_2SnCl_2	780	91 ± 3	92 ± 3	–	–	–	–	–
	2340	–	–	106	101	97	95	80
Ph_4Sn	780	86 ± 5	85 ± 5	–	–	–	–	–
	2340	–	–	113	92	93	90	84
Control value (g)	–	20.1 ± 0.6	0.11 ± 0.01	–	–	–	–	–
Average SE values	–	–	–	9	3	2	3	9

[a] Data are the mean and SE (standard error) values based on 10 young mice (initial weight 13.6 ± 0.3 g) for each treatment after 7 days on treated diets.
[b] Data are the mean and SE values based on four mature mice (initial weight 28.3 ± 0.5 g) for each treatment after 4 days on treated diets.
[c] Control spleen weight, 196 ± 7 mg.
[d] Control blood composition: 15.9 ± 0.2 g Hb/100 ml; 48.9 ± 0.7% Hec; 7.1 ± 0.3 × 10^6 erythrocytes/mm^3; 23 ± 2 × 10^3 total leukocytes/mm^3.
[e] Hb, hemoglobin content.
[f] Hec, hematocrit value.

the blood composition – reduction in lymphocytes and total leukocytes and an increase in erythrocytes, hemoglobin level and hematocrit value – and resulted in a loss in heart, liver, spleen weight and body weight (Table 1) with mature mice feeding for 4 days on diets containing 260 μequiv. organotin/kg, whereas $(Bu_3Sn)_2O$ (TBTO) and $[(PhCMe_2CH_2)_3Sn]_2O$ (Vendex®), were less potent, requiring dietary levels of 780 and 2340 μequiv./kg, respectively, for pronounced effects. The organotin compounds, viz. $PhSnCl_3$, Ph_2SnCl_2 and Ph_4Sn, had little or no effect even at a 2340 μequiv./kg diet.[94] The R_3Sn^+-induced reduction in heart and liver weights of young mice is generally proportional to the reduction in body weight (Table 1). The large amount of lymphatic tissues in the spleen and its importance in formation and destruction of blood cells suggest that action at this site may impair the immunity mechanisms of the animal, reduce the ability to disintegrate aged erythrocytes, and possibly produce a stress condition. These changes could also be a response to stress resulting from other causes such as inhibition of oxidative phosphorylation by the triorganotin compounds.

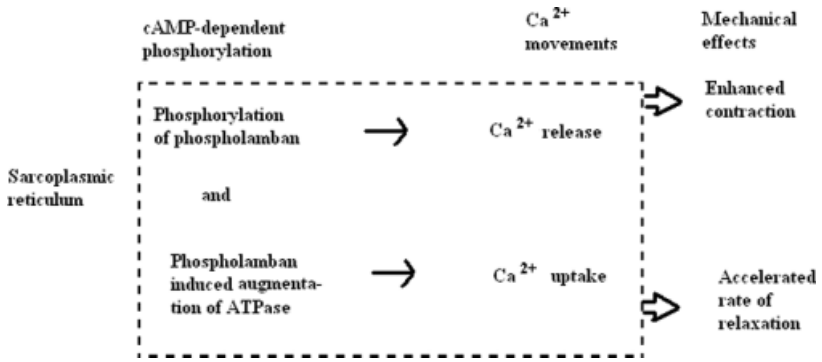
Further, Krajnc *et al*. reported a significant loss of heart weight, following TBTO treatment[81] to male and female Wistar rats at 0, 5, 20, 80 or 320 mg/kg diet for 4 weeks. In the groups of rats receiving 80 or 320 mg TBTO/kg, microcyctic anemia was found. The white blood cell counts were decreased, due to reduction in the number of lymphocytes in the 80 (males) and 320 mg TBTO/kg groups. Changes in hemocytometric values for both sexes (Table 2) comprised a decreased hemoglobin concentration and hematocrit value from 80 mg/kg onward, while at 320 mg/kg the erythrocyte concentration also was reduced. The mean corpuscular volume (MCV) and the mean corpuscular hemoglobin mass (MCH) were lowered in the same dose groups, whereas the mean corpuscular hemoglobin concentration (MCHC) remained unchanged.[81] The leukocyte concentration was decreased in groups fed 80 mg/kg (males) and 320 mg/kg (males and females).

The sarcoplasmic reticulum (SR) calcium pump together with phosphorylation of specific proteins has an important role in myocardial contraction and relaxation.[108] Phospholamban, a 20–24 kDa proteolipid,[109] is phosphorylated by cAMP-dependent protein kinase[110] as well as calmodulin-dependent protein kinase.[111] Phosphorylation of this protein results in stimulation of Ca^{2+}-ATPase and Ca^{2+} transport by the SR (Scheme 1).[110,112] Therefore, active calcium transport by cardiac SR has a key role in the excitation–contraction coupling of the myocardium, where Ca^{2+} release from the SR induces contraction and re-accumulation of Ca^{2+} by the SR leads to relaxation[108,110] (Scheme 1). If any compound alters SR calcium transport, it obviously affects the normal functioning of the heart.

Table 2. Hematological parameters in male and female wistar rats exposed to TBTO[a]

		Dietary concentration (mg/kg)			
Wistar rat	Control	5	20	80	320
Males					
Body weight	245	240	241	226*	113***
Heart	0.76	0.75	0.76	0.73	0.47***
Hemoglobin (mmol/l)	9.7	9.6	9.8	8.9**	8.2***
Hematocrit value (l/l)	0.42	0.42	0.42	0.39	0.35***
Erythrocytes (10^{12}/l)	7.7	7.7	7.8	7.6	7.1*
MCV (fl)	55	54	54	51**	50***
MCH (amol)	1260	1240	1250	1180**	1160***
MCHC (mmol/l)	23	23	23	23	23
Leukocytes (10^6/l)	12 360	12 480	11 420	10 500**	7080***
Lymphocytes	11 186	11 057	10 109	9045**	4753***
Females					
Body weight	162	162	167	161	100***
Heart	0.60	0.59	0.58	0.57	0.46***
Hemoglobin (mmol/l)	9.3	9.1	9.1	8.8*	8.2***
Hematocrit value (l/l)	0.41	0.40	0.40	0.39*	0.36***
Erythrocytes (10^{12}/l)	7.5	7.5	7.5	7.5	6.9**
MCV (fl)	55	53*	54	52***	52**
MCH (amol)	1240	1220	1230	1180**	1190*
MCHC (mmol/l)	23	23	23	23	23
Leukocytes (10^6/l)	9840	8780	9140	9380	5960***
Lymphocytes	8761	7521	7871	7837	4349***

[a] Rats were exposed for 4 weeks. MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin mass; MCHC, mean corpuscular hemoglobin concentration; values are mean of 10 animals/group; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.



Scheme 1. Biochemical events involved in contraction-relaxation cycle of the heart.[110]

A similar potent concentration-dependent inhibition of both basal- and isoproterenol (a β-adrenergic agonist)-stimulated cardiac SR $^{45}Ca^{2+}$ uptake and Ca^{2+}-ATPase by tricyclohexyltin hydroxide (Plictran)®, an organotin acaricide, with an estimated IC_{50} of 2.5×10^{-8} M has been reported[113] by Sahib and Desaiah *in vivo* as well as *in vitro* in rat heart ventricular membrane vesicles. Since cardiac relaxation is mediated by β-adrenergic stimulation via Ca^{2+} uptake by the SR, the inhibition of calcium pump activity by Plictran® may result in alteration in cardiac Ca^{2+} fluxes, leading to cardiac dysfunction. In order to evaluate the mechanism of inhibition of Ca^{2+}-ATPase by Plictran®, the effects of Plictran® on substrate and cationic activation kinetics of β-adrenergic-stimulated cardiac Ca^{2+}-ATPase have also been investigated by Desaiah *et al*.[114] Data indicated alteration of V_{max} and K_m by Plictran® (1.0 and 5.0×10^{-8} M), suggesting a mixed type of inhibition. The β-adrenergic agonist isoproterenol increased V_{max} of both ATP- and Ca^{2+}-dependent enzyme activities. However, the K_m of enzyme was decreased only for Ca^{2+} Plictran®-inhibited isoproterenol-stimulated Ca^{2+}-ATPase activity by altering both V_{max} and K_m of ATP- as well as Ca^{2+}-dependent enzyme activities, suggesting that, after binding to a single independent site, Plictran® inhibits enzyme catalysis by decreasing the affinity of the enzyme for ATP as well as for Ca^{2+}. Preincubation of enzyme with 15 µM cAMP or the addition of 2 mM ATP to the reaction mixture, resulted in slight activation of Plictran®-inhibited enzyme. Pretreatment of SR with 5.0×10^{-7} M propranolol and 5.0×10^{-8} M Plictran® resulted in inhibition of basal activity in addition to the loss of stimulated activity. Further, preincubation of heart SR preparation with 5.0×0^{-5} M coenzyme A in combination with 5.0×10^{-8} M Plictran® partly restored the β-adrenergic stimulation.

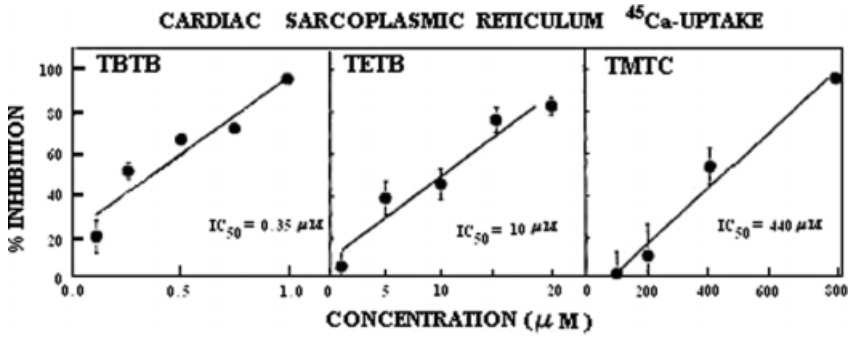


Figure 2. *In vitro* effects of triorganotin compounds on rat cardiac SR ^{45}Ca uptake.[115]

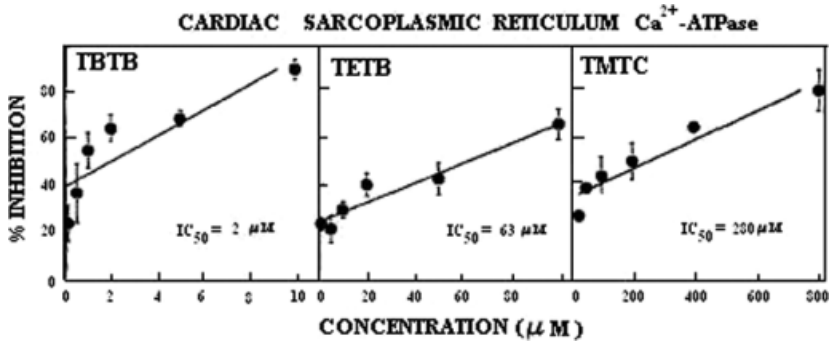


Figure 3. *In vitro* effects of triorganotin compounds on rat cardiac SR Ca^{2+}-ATPase.[115]

These studies suggest that some critical sites common to both basal- and β-adrenergic-stimulated cardiac Ca^{2+}-ATPase are sensitive to binding by Plictran®, and the resultant conformational change may lead to inhibition of β-adrenergic stimulation.[114]

Tri-*n*-butyltin bromide (TBTB), triethyltin bromide (TETB) and trimethyltin chloride (TMTC) inhibited the cardiac SR ^{45}Ca uptake (Fig. 2) and Ca^{2+}-ATPase (Fig. 3) *in vitro* in rat heart in a concentration-dependent manner.[115] The order of potency for Ca^{2+}-ATPase (Fig. 3) as determined by IC_{50}, is TBTB (2 μM) > TETB (63 μM) > TMTC (280 μM). For ^{45}Ca uptake, it followed the same order, i.e. TBTB (0.35 μM) > TETB (10 μM) > TMTC (440 μM). In agreement with the *in vitro* results, both cardiac SR Ca^{2+}-ATPase and ^{45}Ca uptake were significantly inhibited *in vivo* in rats treated with these organotin compounds at all doses, when compared with control rats (Fig. 4), indicating that these tin compounds inhibit cardiac SR Ca^{2+}-transport.[115] Further, TETB and TMTC appeared to exert a dose-dependent effects, while TBTB did not show a dose-response relationship (Fig. 4).

cAMP-dependent ^{32}P-binding to trichloroacetic acid-precipitable cardiac SR proteins in the absence and presence of different concentrations of TBTB, TETB and TMTC are presented in Fig. 5. c-AMP significantly elevated (70–80%) the ^{32}P-binding to SR proteins *in vitro* in the absence of any organotin. In the presence of organotins, cAMP-stimulated ^{32}P-binding to proteins was significantly reduced, but the decrease was concentration-dependent only at lower concentrations (Fig. 5). The order of potency is TBTB > TETB > TMTC. In agreement with *in vitro* studies, cAMP-dependent ^{32}P-binding to proteins was significantly reduced *in vivo* in rats treated with these tin compounds at all doses (Fig. 6).

SDS–polyacrylamide gel electrophoresis of the cardiac SR revealed at least 30 Coomassic blue-stainable bands ranging from 9 to 120 kDa. Autoradiographs from samples incubated in the presence of cAMP indicated ^{32}P incorporation in seven bands. The effects of triorganotins *in vitro* and *in vivo* on cAMP-dependent protein phosphorylation are presented in Figs 7 and 8, respectively. Of the seven bands, the band corresponding to about 24 kDa molecular weight protein (band 3) decreased in its intensity with the treatment of organotin compounds *in vitro* as well as *in vivo*. These results suggest that triorganotin compounds may be affecting Ca^{2+} pumping mechanisms through the alteration of phosphorylation of specific proteins corresponding to phospholamban in rat cardiac SR.[115]

Furthermore, the effects of TBTB, TETB and TMTC on rat cardiac ATPases and catecholamine binding have also been investigated by Desaiah *et al.*,[116] since these phenomena are involved in cardiac function. All three organotin compounds inhibited cardiac Na^+K^+-ATPase, [^{3}H]ouabain binding, K^+-activated *p*-nitrophenyl phosphatase (K^+-PNPPase), and oligomycin-sensitive (o.s.) and oligomycin-insensitive (o.i.) Mg^{2+}- ATPase in a concentration-dependent manner. K^+-PNPPase was less sensitive to these triorganotins when compared with Na^+K^+-ATPase, suggesting that triorganotin compounds affect the Na^+-pump activity by acting on the Na^+-dependent phosphorylation process. Mg^{2+}-ATPase (o.s.) was more sensitive to these triorganotin compounds when compared with Mg^{2+}-ATPase (o.i.), confirming their potent effect on the enzymes of oxidative phosphorylation.[116] The order of potency is TBTB > TETB > TMTC. Further, TETB and TMTC, but not TBTB, inhibited [^{3}H]norepinephrine and [^{3}H]dopamine binding to cardiac membranes in a concentration-dependent manner, the effect being greater with TETB. These results suggest that triorganotin compounds inhibit sodium pump activity as well as ATP synthesis. Since Na^+K^+-ATPase is involved in the active transport of catecholamines, triorganotin compounds not only inhibited the catecholamines transport, but also, to some extent,

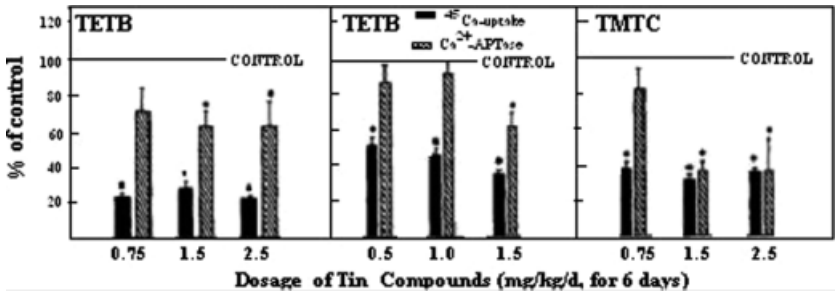


Figure 4. *In vivo* effects of triorganotin compounds on rat cardiac SR ^{45}Ca uptake and Ca^{2+} – ATPase. *Significantly different from control.[115]

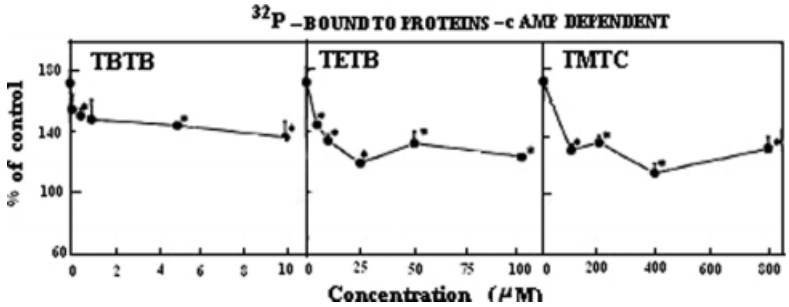


Figure 5. *In vitro* effects of triorganotin compounds on rat cardiac SR protein phosphorylation.[115]

affected catecholamine binding, thus interfering with cardiac function.[116]

Kang *et al*. also reported[69,70] that TET and triphenyltin (TPhT) moieties dose-dependently induced Ca^{2+} release from the isolated sarcoplasmic reticulum membrane vesicles and inhibited the Ca^{2+}-ATPase activity, while TBT had comparatively less potency and efficacy. TPhT induced Ca^{2+} release in ruthenium red-sensitive and insensitive ways, with EC_{50} values of 75 and 270 μM, repectively.[70] TPhT exerted dual effects on the apparent [^{3}H]ryanodine binding; TPhT (0.5–10 μM) dose-dependently potentiated the [^{3}H]ryanodine binding; however, the [^{3}H]ryanodine binding decreased as the concentration of TPhT increased. The dissociation of bound [^{3}H]ryanodine was facilitated by TPhT.

Recently, it has been reported[117] that the exposure to a low-leaching rate TBTO based anti-fouling paint induces significant tachycardia (elevated heart rate) in the sub-tropical mussel, *Perna viridis* (L.) and the response is likely to be associated with organotin detoxication mediated by the action of the heart. A high ratio of TBT : DBT is present in the tissues, suggesting that, although partial detoxication is evident, *P. viridis* is inefficient at metabolizing organotins.[117] As heart serves several homeostatic functions, TBT accumulation and detoxication will be energetically costly and *P. viridis* inhabiting areas that have high shipping densities are likely to experience chronic and sub-lethal stress.[117]

Cardiovascular activity of organotin(IV) derivatives of amino acids

It is an established fact that when a drug is administrated there is a change in blood pressure with the passage of time. Thus, a drug that lowers the blood pressure over a longer duration is considered to be a more effective anti-hypertensive than one with which lowering occurs over a shorter duration. Nath *et al*. investigated cardiovascular activity of a large number of organotin derivatives of amino acids, dipeptides, triglycine, thymidine, ascorbic acid and umbelliferone, when administrated intravenously in either adult cats (body weight 3–4 kg) or mongrel dogs (body weight 10–20 kg) of either gender.[48–54,118–120]

Di-*n*-butyl- and diphenyltin derivatives of L-proline (HPro),[53] triphenyltin derivatives of D-penicillamine (H_2Pen),[48] *trans*-hydroxy-L-proline (HHyp), glutamine (HGlu),[53] tri-*n*-butyltin(Pro) and trimethyltin derivatives of HPro, HHyp and HGlu[53] exhibited mild and delayed anti-hypertensive activity of varying degree

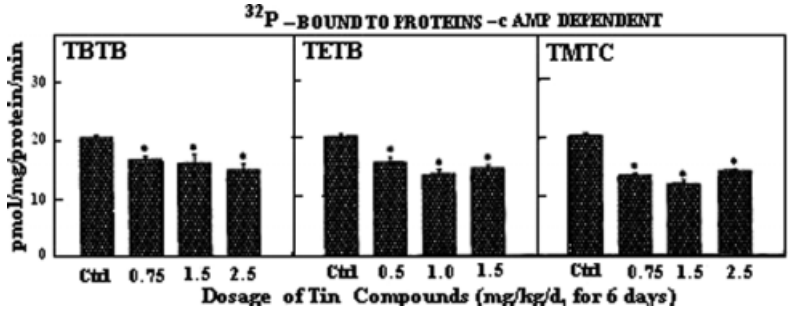


Figure 6. *In vivo* effects of triorganotin compounds on rat cardiac SR protein phosphorylation. *Significantly different from control.[115]

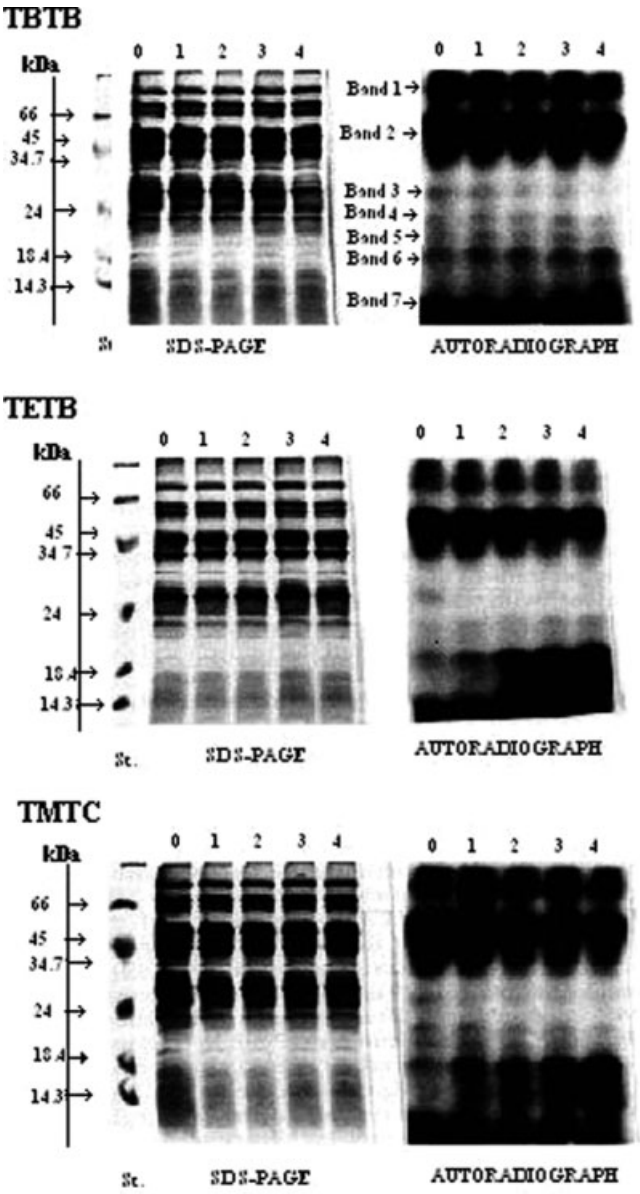


Figure 7. *In vitro* effects of tributyltin bromide (TBTB), triethyltin bromide (TETB) and trimethyltin chloride (TMTC) on cAMP-dependence of a specific protein in rat cardiac sarcoplasmic reticulum. Molecular weight standards (St.) used were bovine plasma albumin (66 kDa), egg albumin (45 kDa), pepsin (34.7 kDa), 13-lactoglobulin (18.4 kDa) and lysozyme (14.3 kDa). The 0–4 indicate concentrations at 0, 0.1, 0.5, 1 and 10 μM for TBTB; 0, 5, 10, 20, 100 μM for TETB; and 0, 50, 100, 200, 400 μM for TMTC. A 50 μg aliquot of SR protein was placed on 15% acrylamide gels. Bands 1–7 indicate ^{32}P-phosphorylated proteins ranging from high to low molecular weight.[115]

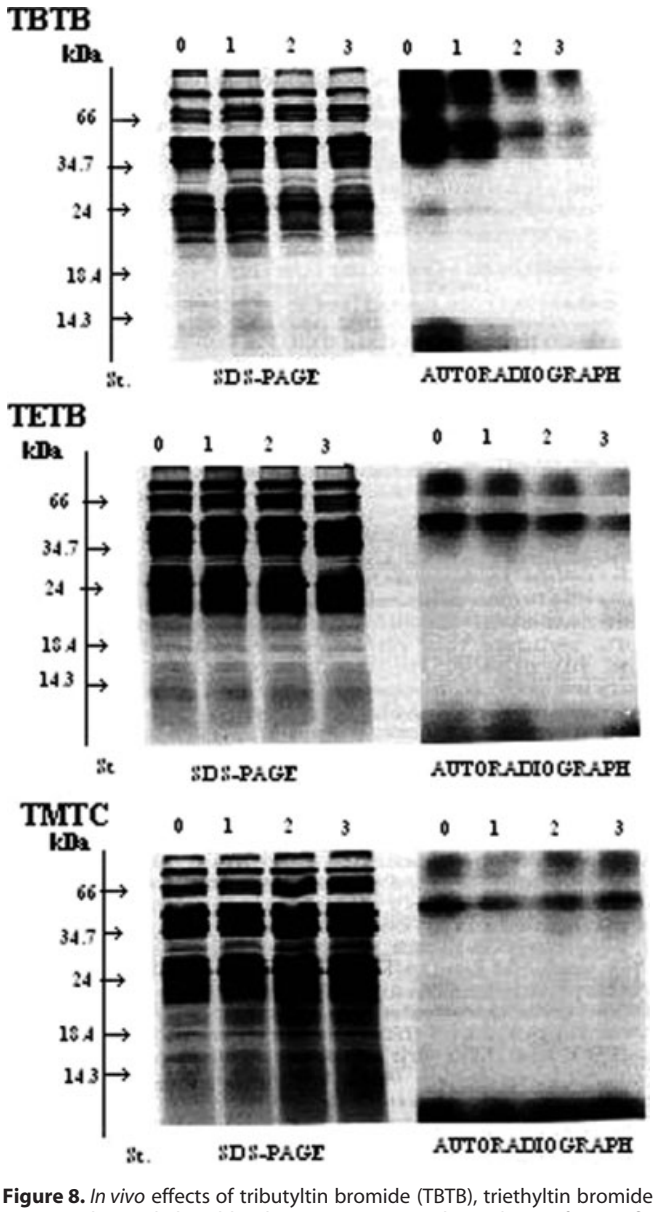


Figure 8. *In vivo* effects of tributyltin bromide (TBTB), triethyltin bromide (TETB) and trimethyltin chloride (TMTC) on cAMP-dependence of a specific protein in rat cardiac sarcoplasmic reticulum. The rats were treated orally with triorganotins for 6 days at a dose of 0 (0), 0.75 (1), 1.5 (2) and 2.5 (3) mg/kg/day in the case of TBTB or TMTC and 0 (0), 0.5 (1), 1 (2) and 1.5 (3) mg/kg/day in the case of TETB. At 24 h after the last dose, rats were sacrificed, heart ventricles were removed and SR were prepared. All the other details were similar to those mentioned in the legend for Fig. 7.[115]

and duration without affecting the carotid occlusion (CO) and noradrenaline (NA) pressure responses (Table 3). Also, none of the studied complexes had shown bradycardia (decrease in heart beat rate) as well as tachycardia, and hence no change in the resting heart beat rate. This suggests that these complexes may act as direct vasodilators on the smooth muscles of blood vessels.

$Ph_2Sn(Pen)$, $Ph_2Sn(Hyp)_2$, n-$Bu_2SnCl(HPen)\cdot H_2O$ and n-$Bu_2Sn(Pen)$ showed potent anti-hypertensive activities.[48,53] In the case of $Ph_2Sn(Hyp)_2$,[53] the initial fall in blood pressure (30 mmHg) was further followed by a potent and gradual decrease in blood pressure (90 mmHg), that lasted for 60 min, and a bradycardia (decrease in heart rate) of 2–3 beats per min was observed. In addition, it was associated with inhibition of the carotid occlusion (CO) without affecting the noradrenaline (NA) response, which might be suggestive of a central site of action for this complex. Considering its potentiality, it was further studied in detail at three gradual doses (1.25, 2.50 and 5.0 mg/kg i.v.). At a dose of 1.25 mg/kg i.v., it showed a transient fall of 10 mmHg followed by a potent fall of 45 mmHg in blood pressure, and no change in heart rate was observed. This complex partially inhibited the CO response without affecting the NA response. At a higher dose (5.0 mg/kg i.v.), this complex initially elicited a marked hypotensive activity (60 mmHg) followed by a very potent fall in blood pressure (120 mmHg) that lasted for about 90 min, and a bradycardia of 5–6 beats per min was

also observed. In addition, there was a complete blockage of pressor responses evoked either by bilateral carotid occlusion (CO) or noradrenaline injection (NA).[53] However, the behavior of $Ph_3Sn(HPen)\cdot H_2O$ and $n\text{-}Bu_2SnCl(HPen)\cdot H_2O$ was different,[48] as $Ph_3Sn(HPen)\cdot H_2O$ showed an immediate fall in blood pressure (−20 mmHg), followed by moderate and gradual increase (+9 mmHg) in blood pressure that lasted for about 9 min and was associated with inhibition of both CO and NA responses, which might be suggestive of the a peripheral site of action, whereas $n\text{-}Bu_2SnCl(HPen)\cdot H_2O$ showed an immediate fall in blood pressure of ∼51 mmHg in ∼20 min without affecting the CO and NA responses.[48]

Table 3. Cardiovascular activity data of organotin(IV) derivatives of amino acids

		Cardiovascular activity[a]			
			Change in blood pressure (mmHg)		
Complex/reference drug	LD_{50} (mg/kg)	Dose (mg/kg)[b] i.v.	Immediate	Delayed	Duration (min)
$n\text{-}Bu_2Sn(Pen)$	>500	2	NC	−40	20
$Ph_2Sn(Pen)$	>500	2	NC	−50	45
$Ph_3Sn(HPen)$	>500	1	NC	−10	5
$Ph_3Sn(HPen)\cdot H_2O$	>1000	2.5	−20 (126.2 ± 4.32)[c,d]	+9 (134.6 ± 6.37)[c]	9 (8.8 ± 1.92)[c]
$n\text{-}Bu_2SnCl(HPen)\cdot H_2O$	>1000	2.5	−51 (81.6 ± 9.07)[c,e]	NC	20 (19.6 ± 1.67)[c]
$n\text{-}Bu_3Sn(Pro)$	n.d.	5	NC	−10	4
$Me_3Sn(Pro)$	n.d.	5	NC	−7	3
$n\text{-}Bu_2Sn(Pro)_2$	n.d.	5	NC	−10	5
$Ph_2Sn(Pro)_2$	n.d.	5	NC	−5	2
$Me_3Sn(Hyp)$	n.d.	5	NC	−5	2
$Ph_3Sn(Hyp)$	>1000	5	NC	−6	6
$Ph_2Sn(Hyp)_2$	>2000	2.5	−30	−90	60
$Me_3Sn(Glu)$	n.d.	5	NC	−5	1
$Ph_3Sn(Glu)$	>1000	5	NC	−6.5	9
Captopril	n.d.	2.5	−10	−60	1440

[a] In comparison to control; [b] i.v., intravenously; NC, no change; [c] mean ± standard error; [d] control 145.6 ± 6.5; [e] control 132.6 ± 7.88; $p < 0.05$; animals: either adult mongrel dogs (body weight 10–20 kg) or cats (body weight 3–4 kg) of either gender.

Table 4. Cardiovascular activity data of diorganotin(IV) derivatives of dipeptides and triglycine

		Cardiovascular activity				
			Change in blood pressure (mmHg)[b,c] (mean ± SE)			Duration (min) (mean ± SE)
Reference drug/complex	LD_{50} (mg/kg)	Dose (mg/kg)[a] i.v.	Control	Immediate	Delayed	
Captopril	–	2.5	160.0 ± 9.45	150.0 ± 6.95	100.0 ± 10.45[d]	1440 ± 30.0
$n\text{-}Bu_2Sn(Gly–Trp)$	>500	2.0	134.8 ± 4.42	NC	124.9 ± 4.87[e]	5.0 ± 1.38
$Ph_2Sn(Gly–Trp)$	>500	2.0	136.4 ± 6.24	NC	116.8 ± 6.54[f]	10.0 ± 1.94
$n\text{-}Bu_2Sn(Val–Val)$	>400	2.0	135.2 ± 4.21	NC	105.4 ± 4.94[e]	10.0 ± 1.85
$Ph_2Sn(Val–Val)$	>300	1.0	131.4 ± 5.96	NC	111.6 ± 5.25[e]	15.0 ± 1.75
$n\text{-}Bu_2Sn(Ala–Val)$	>500	2.0	131.6 ± 5.08	NC	91.8 ± 5.45[e]	20.0 ± 1.45
$Ph_2Sn(Ala–Val)$	>400	2.0	137.4 ± 6.44	NC	117.6 ± 6.14[e]	10.0 ± 1.65
$n\text{-}Bu_2Sn(Gly–Tyr)$	>500	4.0	137.1 ± 4.52	NC	107.5 ± 4.38[e]	5.0 ± 1.15
$Ph_2Sn(Gly–Phe)$	>200	1.0	136.8 ± 5.12	NC	121.6 ± 5.63[e]	10.0 ± 1.67
$n\text{-}Bu_2Sn(Leu–Tyr)$	>800	2.0	145.4 ± 4.86	NC	95.6 ± 4.75[e]	35.0 ± 1.44
$n\text{-}Bu_2Sn(Leu–Leu)$	>400	2.0	132.6 ± 4.31	NC	112.7 ± 4.75[e]	10.0 ± 1.24
$Ph_2Sn(Leu–Ala)$	>200	1.0	148.9 ± 5.72	g	g	5.0 ± 1.20
$n\text{-}Bu_2Sn(Ala–His)$	>500	2.0	138.4 ± 7.42	NC	117.9 ± 4.85[f]	10.4 ± 1.08
$Ph_2Sn(Ala–His)$	>500	2.0	134.8 ± 8.02	NC	104.4 ± 7.35[f]	10.1 ± 1.39
$n\text{-}Bu_2Sn(HGly–Gly–Gly)$	>500	2.0	133.8 ± 7.94	NC	118.6 ± 8.21[f]	5.0 ± 1.82
$n\text{-}Bu_2SnCl(H_2Gly–Gly–Gly)\cdot H_2O$	>1000	2.5	135.0 ± 7.90	60.0 ± 8.09	120.0 ± 8.39[f]	28.6 ± 2.19
$Ph_2Sn(HGly–Gly–Gly)\cdot MeOH$	>500	2.0	131.6 ± 6.31	NC	91.8 ± 6.53[e]	20.2 ± 0.94

[a] i.v., Intraveneously; [b] no change in heart rate (bpm), except $n\text{-}Bu_2SnCl(H_2Gly–Gly–Gly)\cdot H_2O$; [c] no effect on carotid occlusion and noradrenaline pressor responses except $n\text{-}Bu_2SnCl(H_2Gly–Gly–Gly)\cdot H_2O$; SE denotes the standard error; [d] $p < 0.001$; [e] $p < 0.05$; [f] $p < 0.01$; g, immediate fall in blood pressure (−160 mmHg) was observed; animals: either adult mongrel dogs (body weight 10–20 kg) or cats (body weight 3–4 kg) of either gender.

Table 5. Cardiovascular activity data of triorganotin(IV) derivatives of dipeptides and triglycine

Reference drug/complex	LD_{50} (mg/kg)	Cardiovascular activity				
		Dose (mg/kg)[a] i.v.	Change in blood pressure (mmHg)[b,c] (mean ± SE)			Duration (min) (mean ± SE)
			Control	Immediate	Delayed	
Captopril	–	2.5	160.0 ± 9.45	150.0 ± 6.95	100.0 ± 10.45[d]	1440 ± 30.0
n-Bu_3Sn(HGly–Trp)	>1000	2.5	129.6 ± 7.95	NC	123.6 ± 7.89[e]	5.6 ± 0.89
Me_3Sn(HVal–Val)	>1000	2.5	137.6 ± 7.66	129.0 ± 6.55[f]	118.2 ± 6.18[d]	29.2 ± 2.28
Ph_3Sn(HVal–Val)	>500	1.0	140.4 ± 6.84	NC	100.2 ± 6.21[f]	60.0 ± 1.03
Me_3Sn(HAla–Val)	>1000	2.5	132.2± 8.13	122.0 ± 8.68[e]	113.0 ± 6.32[d]	9.2 ± 2.28
Ph_3Sn(HAla–Val)	>2000	1.25	135.0 ± 7.90	125.0 ± 7.38[f]	105.0 ± 7.38[d]	59.6 ± 1.67
		2.5	143.2 ± 8.16	114.0 ± 6.74[f]	74.0 ± 6.81[d]	119.4 ± 2.19
		5.0	130.0 ± 7.90	79.6 ± 8.38[f]	20.0 ± 7.38[d]	149.6 ± 1.67
Me_3Sn(HGly–Tyr)	>1000	2.5	131.2 ± 10.25	NC	71.0 ± 11.18[e]	39.6 ± 2.19
n-Bu_3Sn(HGly–Tyr)	>1000	2.5	137.0 ± 8.42	NC	107.8 ± 7.88[e]	9.6 ± 2.60
Ph_3Sn(HGly–Tyr)	>1000	2.5	139.6 ± 8.64	110.4 ± 8.17[e]	125.8 ± 6.26[f]	40.2 ± 3.49
n-Bu_3Sn(HGly–Gly)	>1000	2.5	130.0 ± 7.90	NC	119.4 ± 8.41[e]	3.6 ± 1.14
Ph_3Sn(HGly–Gly)	>600	2.5	147.8 ± 6.49	64.8 ± 6.41[e]	128.5 ± 4.66[e]	59.8 ± 2.86
Me_3Sn(HLeu–Tyr)	>1000	2.5	133.2 ± 6.45	NC	84.0 ± 4.52[f]	20.0 ± 1.41
Me_3Sn(HLeu–Leu)	>1000	2.5	131.6 ± 6.69	NC	120.4 ± 7.02[f]	9.2 ± 2.28
Ph_3Sn(HLeu–Leu)	>500	1.0	139.4 ± 5.43	NC	109.3 ± 5.03[e]	30.0 ± 2.09
Me_3Sn(HLeu–Ala)	>1000	2.5	131.6 ± 6.98	NC	122.6 ± 4.83[f]	5.4 ± 1.14
n-Bu_3Sn(HLeu–Ala)	>1000	2.5	133.8 ± 9.80	NC	121.4 ± 9.60[e]	5.2 ± 1.09
Ph_3Sn(HLeu–Ala)	>400	1.0	136.4 ± 6.24	NC	111.3 ± 5.93[e]	40.0 ± 1.39
Me_3Sn(HGly–Leu)	>1000	2.5	137.6 ± 8.29	118.4 ± 7.40[d]	108.4 ± 6.54[e]	24.0 ± 3.08
n-Bu_3Sn(HGly–Leu)	>1000	2.5	132.2 ± 6.01	NC	127.2 ± 6.37[e]	4.6 ± 1.14
Ph_3Sn(HGly–Leu)	>500	1.0	135.8 ± 7.89	NC	115.6 ± 6.84[e]	20.0 ± 1.20
Me_3Sn(HGly–Ile)	>1000	2.5	132.0 ± 7.04	NC	92.8 ± 6.41[e]	41.4 ± 2.60
n-Bu_3Sn(HGly–Ile)	>1000	2.5	141.4 ± 9.20	NC	131.4 ± 10.23[e]	9.2 ± 2.28
Ph_3Sn(HGly–Ile)	>500	1.0	142.0 ± 8.43	NC	97.1 ± 7.92[e]	40.0 ± 2.17
Ph_3Sn(HGly–Val)	>600	1.0	138.2 ± 11.54	104.6 ± 11.61[e]	123.0 ± 10.36[e]	49.6 ± 1.67
Ph_3Sn(HAla–His)	>400	1.0	139.6 ± 9.46	NC	104.2 ± 7.48[e]	40.2 ± 1.26
$Ph_3Sn(H_2Gly–Gly–Gly)\cdot H_2O$	>400	1.0	140.2 ± 6.48	NC	120.1 ± 6.89[e]	20.4 ± 3.64

[a] i.v., Intraveneously; [b] no change in heart rate (bpm), and no effect on noradrenaline (NA) pressor response; [c] no effect on carotid occlusion (CO) pressor response, except Ph_3Sn-(HGly–Tyr), Ph_3Sn(HGly–Gly) and Ph_3Sn(HGly–Val); SE denotes the standard error; [d] $p < 0.001$; [e] $p < 0.05$; [f] $p < 0.01$.

Cardiovascular activity of organotin(IV) derivatives of dipeptides, triglycine and thymidine

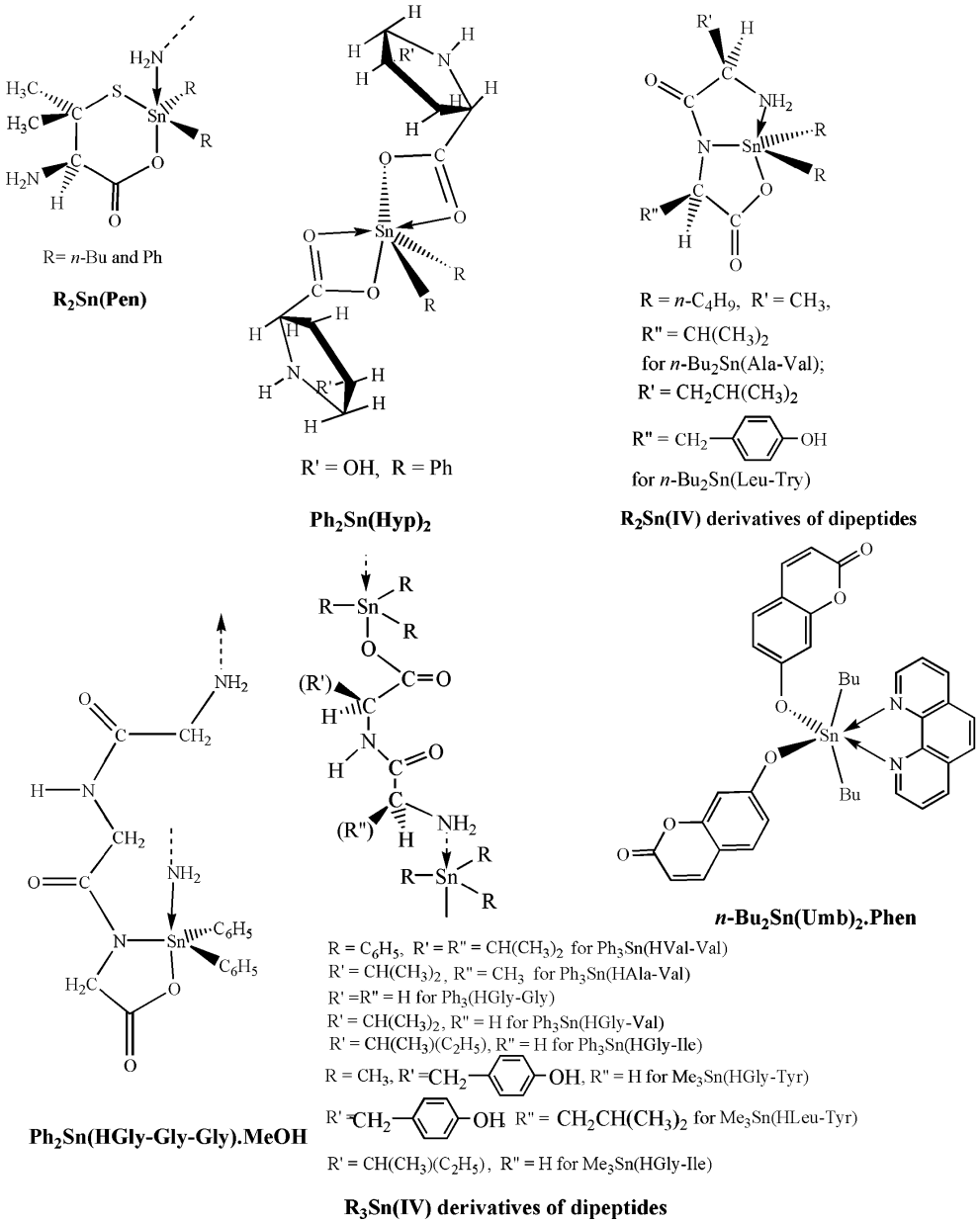
Di- and tri-organotin(IV) derivatives of a large number of dipeptides,[48,50,52,54,118] viz. glycyltryptophane (H_2Gly–Trp), valylvaline (H_2Val–Val), alanylvaline (H_2Ala–Val), glycyltyrosine (H_2Gly–Tyr), glycylphenylalanine (H_2Gly–Phe), leucyltyrosine (H_2Leu–Tyr), leucylleucine (H_2Leu–Leu), leucylalanine (H_2Leu–Ala), β-alanyl-L-histidine or carnosine (H_2Ala–His), glycylglycine (H_2Gly–Gly), glycylleucine (H_2Gly–Leu), glycylisoleucine (H_2Gly–Ile), glycylvaline (H_2Gly–Val) and triglycine (H_3Gly–Gly–Gly), except Ph_2Sn(Leu–Ala),[118] Me_3Sn–(HVal–Val)/(HAla–Val)/(HGly–Leu),[50] Ph_3Sn–(HAla–Val)/(HGly–Tyr)/(HGly–Gly)/(HGly–Val),[52] *n*-Bu_2SnCl–$(H_2Gly–Gly–Gly)\cdot H_2O$[48] and $Ph_3Sn(H_2Gly–Gly–Gly)\cdot H_2O$,[48] exhibited delayed anti-hypertensive activity of varying degree and duration (Tables 4 and 5) without affecting the CO and NA pressure responses, which suggests that these complexes may act as direct vasodilator on the smooth muscles of blood vessels. Moreover, none of these complexes induced bradycardia as well as tachycardia. Furthermore, among Ph_2Sn(IV) derivatives, Ph_2Sn(Ala–His) is found to be the most effective and among *n*-Bu_2Sn(IV) derivatives, *n*-Bu_2Sn(Leu–Tyr) is found to be the most effective.[118] However, an immediate drop of 160 mmHg compared with control has been observed in Ph_2Sn(Leu–Ala) at a dose of 1.0 mg/kg i.v. causing the death of the animal due to cardiac arrest. This compound was very toxic having LD_{50} > 200 mg/kg. In general, the di-*n*-butyltin derivatives exhibited greater anti-hypertensive activity than the diphenyltin derivatives.

The behavior of Ph_3Sn-(HGly–Tyr)/(HGly–Gly)/(HGly–Val) is different, as they showed immediate moderate to potent fall in blood pressure (~30–83 mmHg) as compared with control value, followed by moderate and gradual increase in blood pressure (~15–64 mmHg) that lasted for about 40–60 min and was associated with inhibition of the CO response without affecting the NA response, which might be suggestive of a central site of action.[52] Moreover, Ph_3Sn(HGly–Tyr) and Ph_3Sn(HGly–Gly) induced bradycardia (4–5 beats per min), while Ph_3Sn(HGly–Val) first induced bradycardia followed by a decrease in the resting heart beat rate (tachycardia). Further, Me_3Sn-(HVal–Val)/(HAla–Val)/(HGly–Leu),[50] and Ph_3Sn(HAla–Val)[54] showed an immediate fall in blood pressure (~9–30 mmHg) at a dose of 2.5 mg/kg i.v. as compared with control value, that lasted for 9–120 min without affecting the CO and NA responses and heart rate, except Ph_3Sn(HAla–Val).

However, Ph_3Sn(HAla–Val) decreased the heart rate by 5 beats per min. Since this complex showed promising anti-hypertensive activity, it was further assayed at three gradual doses (1.25, 2.5 and 5.0 mg/kg i.v.). These data indicated that it lowered blood pressure by 110 mmHg in 150 min at 5.0 mg/kg dose (Table 5).[54]

These observations indicate that the anti-hypertensive activity is influenced by the structural features of the side chain at the methylene carbon atom adjacent to either O–C=O and/or amino group in the dipeptide anion coordinated to the di- and triorganotin(IV) moiety, as well as on the tin-bound organic group. In general, the di-*n*-butyltin(IV) dipeptides exhibited greater anti-hypertensive activity than the diphenyltin analogs, whereas the Ph_3Sn(IV) derivatives showed potent activity of longer duration than the Me_3Sn(IV) and *n*-Bu_3Sn(IV) analogs. In the case of *n*-$Bu_2SnCl(H_2Gly–Gly–Gly)\cdot H_2O$, an immediate fall in blood pressure (~75 mmHg) was followed by a moderate and gradual increase in blood pressure (~60 mmHg) that lasted for ~29–30 min and was associated with inhibition of both CO and NA responses, which might be suggestive of a peripheral site of action.[48] Further, it first decreased the resting heart rate (3–4 beats per min) followed by an increase in it (3–4 beats per min). $Ph_3Sn(H_2Gly–Gly–Gly)\cdot H_2O$ showed a fall in blood pressure of ~20 mmHg in 20 min and inhibited the CO, but potentiated the NA pressure response.[48]

Triphenyltin thymidinate exhibited insignificant anti-hypertensive activity (a drop of 5 mmHg of blood pressure as compared to control) that lasted for 2 min without causing any effect on the heart rate, CO and NA pressure responses.[49] Some of triphenyltin(IV) or trimethyltin(IV) derivatives of dipeptides, viz. Ph_3Sn(HVal–Val), Ph_3Sn(HAla–Val), Ph_3Sn(HGly–Ile), Ph_3Sn(HGly–Val), Ph_3Sn(HGly–Gly), Me_3Sn(HGly–Tyr), Me_3Sn(HGly–Ile) and Me_3Sn(HLeu–Tyr) (Scheme 2) have exhibited potent anti-hypertensive activity, comparable to that



Scheme 2. Structures of organotin(IV) derivatives exhibiting potent cardiovascular activity.

Table 6. Cardiovascular activity data of organotin(IV) derivatives of umbelliferone and their 1,10-phenanthroline adducts

Reference drug/complex	LD_{50} (mg/kg)	Cardiovascular activity[a]				
		Change in HR	Change in blood pressure (mm Hg) (mean ± SE)			Duration (min) (mean ± SE)
			Control	Immediate	Delayed	
Captopril	–	–	160.0 ± 9.45	150.0 ± 6.95	100.0 ± 10.45	1440 ± 30.0[e]
$Me_3Sn(Umb)$[b]	>1000	–	132.0 ± 6.7	122.0 ± 6.4[g]	–	4.9 ± 1.1
$Ph_3Sn(Umb)$[b]	>1000	–	131.8 ± 10.0	112.4 ± 8.2[e]	–	12.4 ± 2.5
n-$Bu_2Sn(Umb)_2$[b]	>1000	–	135.0 ± 14.6	115.6 ± 13.2[f]	–	13.8 ± 2.2
$Ph_2Sn(Umb)_2$[b]	>1000	–	138.4 ± 6.3	118.4 ± 5.4[f]	–	10.0 ± 2.4
$Me_3Sn(Umb)\cdot Phen$[c]	>1000	↓↑	137.0 ± 6.6	117.6 ± 4.6[f]	–	13.2 ± 3.3
$Ph_3Sn(Umb)\cdot Phen$[d]	>1600	↓↑	143.8 ± 9.6	120.0 ± 7.2[e]	124.0 ± 9.3[f]	16.2 ± 1.3
n-$Bu_2Sn(Umb)_2\cdot Phen$[c]	>1000	↓↑	135.0 ± 7.9	60.6 ± 6.8[f]	104.6 ± 9.2[e]	45.0 ± 2.2

[a] Dose = 2.5 mg/kg i.v. (intraveneously); [b] no effect on carotid occlusion and noradrenaline pressor responses; [c] inhibited CO and NA responses; [d] no effect on carotid occlusion but inhibited NA response; [e] $p < 0.001$; [f] $p < 0.05$; [g] $p < 0.01$; SE denotes the standard error; HR denotes heart rate (bpm); ↓ decrease in heart beat rate, ↑ increase in heart beat rate.

of Captopril, but the duration of efficacy is much shorter than that for Captopril. Since these compounds have low toxicity (LD_{50} > 1000–2000 mg/kg), they may be considered as good anti-hypertensive drugs.

Cardiovascular activity of organotin(IV) derivatives of ascorbic acid and umbelliferrone

Organotin(IV) ascorbates exhibited mild anti-hypertensive activity (a fall of 6–10 mmHg in blood pressure) which lasted for 3–5 min only, at a dose of 5.0 mg/kg i.v., without affecting the CO and NA responses; thus it can be said that these compounds do not change blood pressure appreciably.[119]

Di- and tri-organotin(IV) derivatives of umbelliferrone exhibited mild anti-hypertensive activity of varying degree and duration without affecting the CO and NA responses.[51,120] Such a profile of pharmacological effect is indicative of the direct vasodialator action of these compounds. The 1,10-phenanthroline adducts of these organotin(IV) derivatives of umbelliferrone exhibited potent anti-hypertensive activity of varying degree and duration. Thus, n-$Bu_2Sn(Umb)_2$.phen showed potent initial hypotensive activity (75 mmHg) of gradual onset (+44 mmHg), which was followed by a bradycardia of 5 beats per min then by tachycardia of 3–4 beats per min (Table 6). The cardiovascular activity of this compound lasted for about 45 min and was associated with marked inhibition of the CO and NA responses.[120] Such a cardiovascular profile is suggestive of a peripheral site of action. $Ph_3Sn(Umb)\cdot$ phen showed hypotensive activity (23 mmHg), which lasted for about 16 min, and inhibited the NA response without affecting the CO response, whereas $Me_3Sn(Umb)\cdot$ phen lowered blood pressure by 20 mmHg with inhibition of both CO and NA responses. Diorganotin(IV) derivatives of umbelliferrone and their 1,10-phenanthroline adducts were found to lower blood pressure more effectively than triorganotin analogs.

Conclusion

The widespread applications of organotin compounds have increased the possibility of their intake by human beings. Triorganotin compounds are the most toxic and affect a variety of biochemical and physiological systems. Their apparent mode of action may vary with the compound and its dose, and the species and route of administration. Trialkyl- and triphenyltin compounds interfere with heme metabolism as well as the cardiovascular system, cause a fall in blood pressure resulting from a depression of the vascular smooth muscle, alter blood composition and result in a decrease in organ : heart ratio in rats and mice. They also inhibit Mg^{2+}-ATPase (o.s.) and Ca^{2+}-ATPase activities in beef heart mitochondria, basal- and isoproterenol-stimulated cardiac sarcoplasmic reticulum (SR) $^{45}Ca^{2+}$ uptake and Ca^{2+}-ATPase *in vivo* as well as *in vitro* in rat heart ventricular membrane vesicles, and sodium pump activity as well as ATP synthesis. These studies indicate that triorganotin compounds may be affecting Ca^{2+} pumping mechanisms through the alteration of phosphorylation of specific proteins corresponding to phospholamban in rat cardiac SR and thus interfering with cardiac function, since SR Ca^{2+} and Na^+ transport are involved in cardiac function. Several di- and tri-organotin derivatives of amino acids, dipeptides, triglycine and umbelliferrone show the potent anti-hypertensive activity comparable to that of Captopril with or without affecting the carotid occlusion and noradrenaline pressure responses and heart rate, but the duration of efficacy is much shorter than that for Captopril. Since these compounds have low toxicity (LD_{50} > 1000–2000 mg/kg), they may be considered as good anti-hypertensive drugs.

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