Similarity of endothelin to snake venom toxin

SIR—We wish to point out the striking functional and structural similarities between porcine endothelin[1] and certain newly isolated toxins from the burrowing asp, *Atractaspis engaddensis*[2]. These sarafotoxins S6 cause cardiac arrest when injected into mice (LD_{50} = 0.01–0.2 μg per gram body weight), probably as a direct result of coronary vasospasm[3]. Similarly, endothelin is reported to be one of the most potent vasoconstrictors known.

The amino-acid sequences of these peptides are remarkably similar (see figure). Both peptides consist of a single

Amino-acid sequences of endothelin and sarafotoxin S6b. One-letter amino-acid code. Boxes sequence identity. Sequence of enothelin from ref. 1 and sequence of sarafotoxin S6b from ref. 2.

21-residue peptide chain containing four cysteines. All four cysteinyl residues appear in identical positions, and the overall sequence homology between endothelin and sarafotoxin S6b is 67 per cent. The peptides almost certainly share a common ancestor.

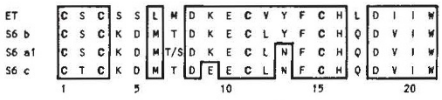
Although the role of endothelin in the porcine cardiovascular system remains to be determined, sarafotoxins S6 function as offensive weapons to rapidly incapacitate prey species. The almost simultaneous discovery of these peptides in such very different circumstances underscores the versatility of nature, and serves as yet another example of the conversion by an organism of a biologically active peptide into a toxic principle.

C. Y. LEE
Department of Pharmacology,
College of Medicine,
National Taiwan University,
Taipei, Taiwan, ROC
VINCENT A. CHIAPPINELLI
Department of Pharmacology,
St Louis University School of Medicine,
St Louis,
Missouri 63104, USA

SIR—We have found an intriguing homology between endothelin (ET), the vasoconstrictor peptide we recently identified[1,4] in the mammalian vascular endothelium, and a group of peptide toxins (sarafotoxins S6) recently purified and sequenced[2] from the venom of Israeli burrowing asp *Atractaspis engaddensis*. All these peptides consist of 21 amino-acid residues with two pairs of half-cystine residues in identical positions and a hydrophobic tail with a carboxy-terminal tryptophan residue (see figure). The strong sequence similarities (52–67 per cent identities or 71–81 per cent identities including conservative substitutions) convincingly suggest that the toxins and ET have a common evolutionary origin.

These peptides resemble each other not only in structure but also in the biological activities. Sarafotoxins S6, like ET, have a potent coronary constrictor activity[3]; their strong cardiac toxicity is chiefly the result of a persistent coronary vasoconstriction. When administered intravenously to mice in doses as low as 10–200 μg kg^{-1}, sarafotoxins S6 cause a severe coronary vasospasm that, accompanied by electrocardiographic changes similar to those seen in severe acute myocardial infarction, eventually leads to cardiac arrest and death[2,5]. We have found that intravenous injection of suprapressor doses of ET is also highly lethal to rats; injection of 10–20 μg kg^{-1} usually kills an animal by severe coronary insufficiency (unpublished observations). The extremely long-lasting vasoconstrictor activity of ET, which is quite difficult to wash out[1], also exemplifies the toxin-like properties of this mammalian peptide.

The existence of cognate peptides of ET in the exocrine venomous glands of snakes suggests that ET, or related peptides, are expressed in mammalian organs other than vascular endothelium. Perhaps a



Alignment of porcine/human endothelin (ET) and several isoforms of sarafotoxins S6 from venom of *A. engaddensis*. Identical and conservatively substituted amino-acid residues enclosed in boxes; half-cystine residues in bold.

number of distinct peptides of the 'ET/sarafotoxin family' will be found in various tissues from a wide range of species. Chemical identification of such peptides would provide an excellent opportunity to investigate the structure–activity relationship as well as the physiological and/or pathophysiological significance of endothelin.

CHIKAHISA TAKASAKI
Department of Chemistry,
Tohoku University,
Sendai 980, Japan
MASASHI YANAGISAWA
SADAO KIMURA
KATSUTOSHI GOTO
TOMOH MASAKI
Institute of Basic Medical Sciences,
University of Tsukuba,
Tsukuba,
Ibaraki 305, Japan

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Negative or positive cloud optical depth feedback?

SIR—Roeckner *et al.*[1] have reported results from a pair of general circulation model (GCM) simulations — a present-day control and a perturbation with the solar constant increased by 2 per cent — in which the cloud optical depth could vary through its dependence on the prognostically calculated cloud liquid water. This simulation pair predicted a 3.3-°C warming of the globally averaged surface-air temperature as a result of the 2 per cent solar constant increase.

To determine the contribution of cloud optical depth feedback to this warming, Roeckner *et al.* calculated the changes in the net radiative fluxes at the tropopause (top of their GCM) and at the Earth's surface, ΔN_t and ΔN_s respectively, that result when the equilibrium climate of the control simulation is modified by replacing the cloud liquid water with its value from the 2 per cent solar constant experiment. The results show that ΔN_t and ΔN_s are then of different sign, ΔN_t being positive and ΔN_s negative. Roeckner *et al.* conclude that "The net effect of clouds is to provide a negative feedback on surface temperature, rather than the positive feedback found in earlier general circulation model studies without considering cloud optical depth feedbacks". But whether or not the cloud optical depth feedback in these simulations is negative depends upon whether the change in the energy balance at the surface, characterized by ΔN_s, dominates the change in the energy balance for the planet, characterized by ΔN_t. If the cooling tendency from the decrease in ΔN_s is greater than the warming tendency from the increase in ΔN_t, the cloud optical depth feedback is negative. If the opposite occurs, the cloud optical depth feedback is positive.

To determine which of these two outcomes is more probable I have performed two control/perturbation simulation pairs with the radiative-convective model (RCM)[2,3]. Other feedbacks included in this model for the present study are the positive feedbacks from water vapour (fixed relative humidity), cloud attitude (fixed cloud-top temperature, 228 K) and surface albedo, and where indicated, negative feedback from moist-adiabatic lapse-rate adjustment. For the control simulation the optical depth τ and emissivity ε of the RCM's single cloud-layer were fixed at τ = 1.11 and ε = 0.62. These values were also used for the perturbation simulation without cloud optical depth feedback. For the perturbation simulation with cloud optical depth feedback, τ and ε were changed by $\Delta\tau$ and $\Delta\varepsilon$, with the values chosen to reproduce the ΔN_t and ΔN_s values for the total cloud liquid-water effect in ref. 1. The