matters arising

No evidence for a central serotonergic mechanism in arrhythmogenic effects of deslanoside

WE would like to comment on some of the data from this laboratory recently published in *Nature*[1]. There is an error in Table 2 of ref. 1 involving the effects of 5,7-dihydroxytryptamine (5, 7-DHT) on the 5-hydroxytryptamine (5-HT) concentration of the medulla-pons, hypothalamus, and colliculi of five cats. The data in Table 2 indicate that 5,7-DHT administered as a single dose of either 100 μg per kg to three cats, or 200 μg per kg to two cats, into the anterior horn of the left lateral ventricle 8 d before intoxication with deslanoside produces significant depletion of 5-HT in each of the three brain areas. Brain areas of seven cats were in fact examined but only data from five animals showed 5-HT depletion, and these data were presented in Table 2. The mean doses of deslanoside required to produce ventricular arrhythmia and ventricular tachycardia (but not ventricular fibrillation) in these five cats were significantly higher than corresponding doses in control animals. Calculation of the doses of deslanoside required to reach these same endpoints in all seven animals revealed no difference between the 5,7-DHT animals when compared with their controls.

The values for the brain 5-HT content of the 5,7-DHT treated animals are in error. We have repeated these experiments and found in seven animals who received 5,7-DHT (200 μg per kg into the anterior horn of the left lateral ventricle 8 d before intoxication with deslanoside), no significant depletion of 5-HT and no change in the doses of deslanoside which produce ventricular arrhythmias. We did find that the 200 μg per kg dose did produce significant depletion of norepinephrine in the hypothalamus. In addition, we have administered a much larger dose of 5,7-DHT (2.0 mg) into the lateral ventricle plus desmethylimipramine intraperitoneally to prevent 5,7-DHT uptake into noradrenergic nerve endings. This treatment resulted in a significant depletion of brain 5-HT but no significant alteration in the dose of deslanoside to produce ventricular arrhythmias.

In conclusion, we have no evidence for a role of central serotonergic mechanisms in the arrhythmogenic effects of deslanoside. However, we are continuing to obtain evidence that a serotonergic mechanism is involved in the arrhythmogenic action of digitalis. Our current data indicate that it is 5-HT located in peripheral tissues and neural tissue outside the blood-brain barrier which may be important[2].

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Repressed motor nerve terminals in normal frog skeletal muscle

GRINNELL ET AL.[1] have demonstrated that when allowing two foreign nerves to innervate a transplanted frog sartorius muscle, control of transmission at neuromuscular junctions on muscle fibres is shared between the two nerves, one being more effective in terms of the quantal content of endplate potentials than the other. However, we previously[2] presented evidence of mutual repression by some axons in muscles with normal innervation. Grinnell *et al.*[3] emphasise both the "quantitative and probable qualitative difference" between their results and ours, and they suggest that one possible explanation for the apparent extensive polyneuronal innervation reported by us (up to 60% of the tension of one of the sharing motor units) is the low Ca^{2+} concentration used by us, 1.08 mM as against their 1.8 mM. Grinnel *et al.* agree with our findings of little or no detectable overlap in a comparison of twitch tensions, and are only challenging our estimates of overlap using tetanic tension. They put the upper limit of tetanic tension overlap at 25%, and in experiments using 1.08 mM Ca^{2+} they found a significant drop in twitch tension but no difference in the 50 per s tetanus tension. It seems to us that if there is no difference in the measured tetanic tension at the two Ca^{2+} concentrations, then other explanations must be sought to account for the differences in amounts of overlap reported by Grinnell *et al.* and ourselves.

We agree that 1.08 mM Ca^{2+} is lower than is usually used, and since at this concentration neuromuscular transmission may begin to be affected (see, for example, ref. 4) we have repeated some of our experiments on sartorius using 1.8 mM Ca^{2+}. None of the data (from 27 units in four experiments) differ significantly from those previously published by us, including both the value of twitch tension and the measurement of overlap. We therefore conclude that the differences in estimated overlap, as measured by us and by Grinnell *et al.* must either be due to the different species of frog used, or because Grinnell *et al.* did not make comparisons between single motor units, but were stimulating bundles of motor axons. We have shown (Fig. 5 in ref. 3) that overlap between motor units is not distributed uniformly throughout the population of units.

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GRINNELL ET AL. REPLY—We find it surprising that there is no difference between the twitch tensions in 1.08 and 1.8 mM Ca^{2+} (ref. 1), since in both *R. catesbeiana* and *R. pipiens* sartorius twitch tension changes sharply with such a Ca^{2+} change. However, accepting the findings of Luff and Proske we agree that the most likely explanation for the difference in our results is a species difference. That junctions in two different muscles can have very different safety factors is shown by the consistent difference we have observed between the sartorius and cutaneous pectoris muscles in the same species (A. G. & A. Herrera, unpublished). Presumably there could be equally large differences between the homologous muscles in two different genera of frogs.

The implication of Luff and Proske's finding is that in *Litoria aurea* overlapping junctions are either suprathreshold at 1.08 mM Ca^{2+}, or so far below threshold that an insignificant number, if

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