Dependence of Skeletal Muscle Vascular Response to Serotonin Upon the Level of Vascular Resistance (37204)

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5-Hydroxytryptamine (5-HT, serotonin) is a naturally occurring, vasoactive agent which produces a variety of effects on the cardiovascular system. Mean systemic arterial blood pressure does not change consistently during intravenous administration of this amine in dogs (1), due apparently to inconsistent changes in peripheral vascular resistance (2, 3). Investigations by Haddy and associates (4, 5) and McCubbin *et al.* (6) indicate that the direction change in peripheral resistance may be conditioned by the initial level of vascular neurogenic "tone". However, further studies by our group (3, 7) suggest that the response of skin vessels to intra-arterially or intravenously administered 5-HT is always a rise in vascular resistance in all segments of dog forelimb or paw skin vasculatures; the response of forelimb muscle or gracilis muscle vasculature may be minimal and irregular and perhaps related to the initial level of resistance.

The objective of the current study was to further investigate the relationship between the initial level of vascular resistance and vascular response to 5-HT in a pure skeletal muscle vascular bed.

Methods. Fifty-two animals were anesthetized with sodium pentobarbital (30 mg/kg), anticoagulated with sodium heparin (3 mg/kg), and ventilated with a Harvard constant volume respirator via an intratracheal tube. A femoral artery was cannulated for arterial blood pressure; all pressures were measured with Statham pressure transducers and a Sanborn direct writing recorder.

Constant flow. A Sigmamotor pump was interposed between the right femoral and gracilis arteries in 32 dogs, which allowed perfusion of the gracilis muscle at constant flow. Blood returned to the dog via the intact gracilis vein. Gracilis artery perfusion and gracilis vein pressure were measured from the arterial inflow tubing distal to the pump and from a side branch of the gracilis vein, respectively. All side branches of the gracilis artery and vein were ligated and the origin and insertion of the muscle were securely tied. 5-HT (serotonin creatinine sulfate) was infused behind the pump at sequentially faster rates over the range 2–100 μg/min.

The muscles were denervated after 5-HT infusion. If initial resistance was high, resistance was then lowered metabolically by causing the muscle to exercise by Faradic stimulation of the gracilis motor nerves (f = 2/sec, d = 5 msec, v = 5 V). If initial resistance was low, resistance was then increased by sympathetic nerve stimulation (f = 10/sec, d = 10 msec, v = 10 V) after prevention of muscle contraction by local intra-arterial infusion of decamethonium (2 mg). In each of these experiments, 5-HT was infused at 50 μg/min, before and during alteration of vascular resistance.

In a final group of 20 dogs, the collateral free gracilis muscle was perfused at natural flow through the uninterrupted gracilis artery. Outflow was measured by graduate cylinder and stopwatch from the cannulated gracilis vein and was returned continually to a cannulated femoral vein with a Sigmamotor pump. 5-HT was infused into a side branch of the gracilis artery over the same dose range as in the Constant Flow group.

Statistical comparisons were made using the Student's t test for comparison of the means and Student's t test modified for within group comparisons. A p value less than 0.05 was considered significant.

Results. Constant flow. Figure 1 shows that in constant flow perfused muscles with low

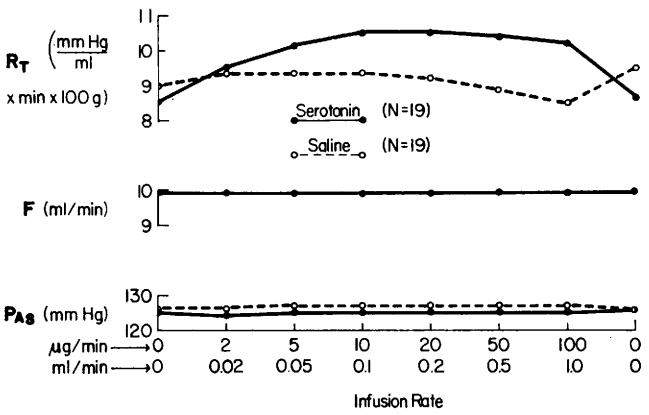

FIG. 1. Effects of intra-arterial serotonin infusion in constant flow perfused gracilis muscles with low initial resistance; R_T = total muscle vascular resistance; F = flow; P_{AS} = mean systemic arterial blood pressure.

initial resistance ($<$ 12.3 units), 5-HT infusion caused a progressive increase in total muscle vascular resistance ($p < 0.05$) as the infusion rate was increased from 2 to 10 γ/min ($p < 0.05$). Increasing the rate further (20, 50, and 100 γ/min) produced no greater average increase in resistance, although resistance remained elevated above the control value ($p < 0.05$). Resistance returned to near control after stopping 5-HT infusion. Equivolume infusions of saline did not alter resistance except at the highest rate of infusion, which caused a slight decrease.

Figure 2 shows that in constant flow perfused muscles with high initial resistance ($>$ 12.3 units), 5-HT infusion caused a decrease in total muscle vascular resistance at the onset of infusion ($p < 0.05$). Resistance decreased progressively as the infusion rate was increased to 100 γ/min and returned to near control level after stopping serotonin infusion. The average decrease in resistance produced at the higher infusion rates (50 and 100 γ/min) was significantly greater than that caused by equivolume infusions of saline ($p < 0.05$).

Figure 3 shows that in the denervated muscle, 5-HT caused a small rise in overall

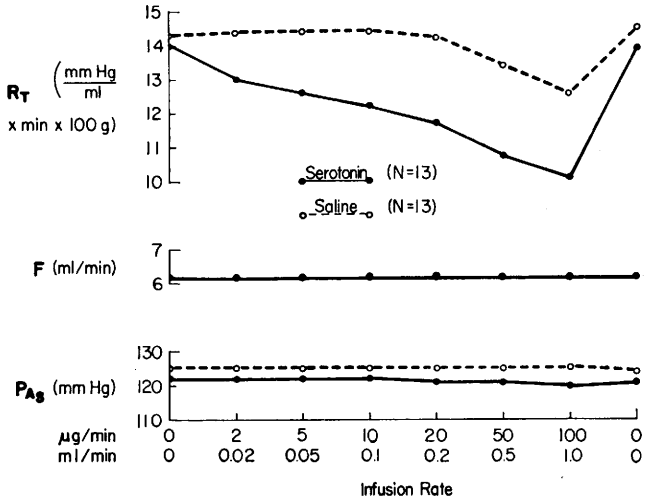

FIG. 2. Effects of intra-arterial serotonin infusion in constant flow perfused gracilis muscles with high initial resistance; R_T = total muscle vascular resistance; F = flow; P_{AS} = mean systemic arterial blood pressure.

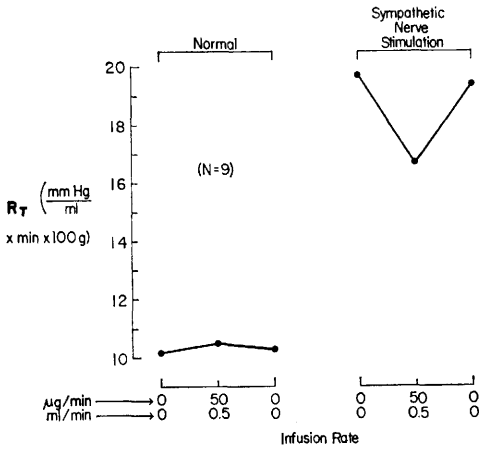

FIG. 3. Effects of intra-arterial serotonin infusion on vascular resistance in constant flow perfused muscles with low initial resistance and with resistance subsequently increased by nerve stimulation; R_T = total muscle vascular resistance.

muscle resistance when the initial resistance was low ($p < 0.05$). However, when resistance in the same muscles was increased to a high level by sympathetic nerve stimulation, 5-HT then caused a marked fall in total vascular resistance ($p < 0.05$). It should be noted that the increment in resistance shown in Figure 3 is substantially less than that in Fig. 1 at comparable infusion rates of 5-HT. This is apparently related to the higher average initial resistance in the denervated group (Fig. 3) than in the low resistance group (Fig. 1).

Figure 4 shows that 5-HT caused a marked drop in muscle vascular resistance when the initial resistance was high ($p < 0.05$). However, when resistance in the same muscles was decreased to a low steady-state level by exercise dilation, 5-HT caused a rise in total vascular resistance in every case ($p < 0.05$).

Natural flow. Resistance changes were similar to those seen in the Constant Flow group. In 8 muscles with a low initial resistance, 5-HT caused a progressive, dose related increase in resistance and fall in flow, with no change in systemic pressure. In 12 muscles with an initial high resistance, 5-HT infusion resulted in opposite changes in resistance and flow.

Discussion. The data indicate that the directional response to locally-infused 5-HT is dependent upon the initial level of vascular resistance and that it can be predictably changed in a given muscle by manipulating the initial vascular resistance. Thus, 5-HT decreases gracilis muscle vascular resistance when initial resistance is high and vice versa. This variable response occurs when the initial resistance is manipulated neurogenically or as a result of metabolically induced vasodilation.

This study extends earlier work from our laboratory (3, 7) which indicated irregular changes in dog forelimb skeletal muscle and gracilis muscle vascular resistance during intra-arterial infusion of 5-HT. However, in the earlier forelimb and gracilis muscle experiments, resistances were not calculated on a unit weight basis,[1] and no attempt was made to alter the spontaneous vascular resistance. Also, while average changes in gracilis muscle resistance were not significant during 5-HT infusion in the gracilis muscle in the earlier studies, changes did occur in individual cases. It is perhaps noteworthy that if all the data in the current study were compiled without regard to the initial level of resistance, the data would show that on the average 5-HT had no significant effect on gracilis muscle vascular resistance. This may have some relevance to earlier reports by us (3) and others (2) regarding an apparent lack of vascular responsiveness of skeletal muscle to 5-HT.

Local administration of 5-HT decreases vascular resistance when initial resistance is neurogenically high and vice versa in the dog forelimb (5), hindlimb (6), kidney (6), and mesentery (8).

Thus, it is clear that the *in vivo* directional vascular resistance response to 5-HT varies inversely with the initial level of resistance in most organs. In contrast, large and moderately sized artery strips from several organs always exhibit an increase in tension when exposed to 5-HT (9, 10), even if the strips respond to acetylcholine or histamine with relaxation (11). These *in vitro* observa-

[1] Resistances computed on a unit weight basis to correct for variations in organ weight allows for more adequate comparison of the degree of constriction in a vascular bed.

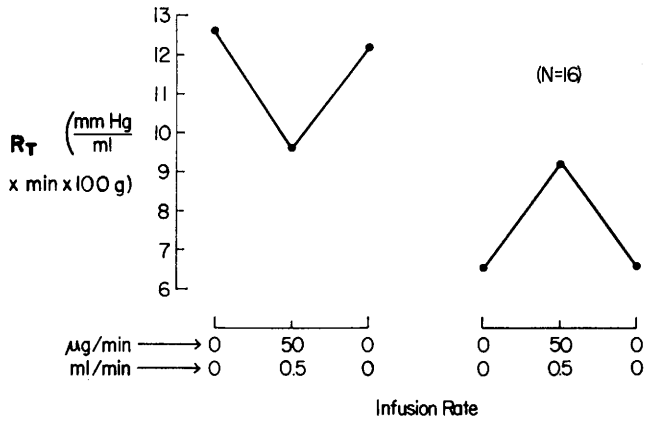

FIG. 4. Effects of intra-arterial serotonin infusion on vascular resistance in constant flow perfused muscles with high initial resistance and with resistance subsequently lowered by exercise dilation; R_T = total muscle vascular resistance. Note: three of the experiments included in this group started with low initial resistance but resistance spontaneously rose during the experiment and hence are included in both low and high resistance groups.

tions and the present study support the explanation of Haddy and associates (5, 8) that the variable response to serotonin results from the differential effect of 5-HT on arteries and arterioles, *i.e.*, 5-HT always constricts large arteries and always dilates arterioles.

Summary. 5-Hydroxytryptamine (5-HT; serotonin) was infused intra-arterially at sequentially faster rates in 52 isolated, collateral-free gracilis muscles of dogs. The rates chosen produced no systemic effects. Both constant (pump perfused) and natural flow experiments were conducted. Serotonin was first tested in muscles with unaltered initial resistance and subsequently in the same muscles after baseline resistance was increased by sympathetic nerve stimulation or lowered by exercise. 5-HT consistently increased vascular resistance in muscles with an initial low resistance. The resistance response (decrease) caused by 5-HT in muscles with an initial high resistance could be reversed by lowering baseline resistance metabolically (exercise). Also, the increase in resistance caused by 5-HT in muscles with an initial low resistance could be reversed by increasing baseline resistance via sympathetic nerve stimulation. These data show that the local vascular response of gracilis muscle to 5-HT is dependent upon the initial level of vascular resistance and imply that this dependency is not exclusively linked to neurogenic tone.

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1. Page, I. H., and McCubbin, J. W., Circul. Res. 1, 354 (1953).

2. Abboud, F. M., Fed. Proc., Fed. Amer. Soc. Exp. Biol. 27, 1391 (1968).

3. Daugherty, R. M., Jr., Scott, J. B., Emerson, T. E., Jr., and Haddy, F. J., Amer. J. Physiol. 214, 611 (1968).

4. Haddy, F. J., Angiology 11, 21 (1960).

5. Haddy, F. J., Gordon, P., and Emanuel, D. A., Circul. Res. 7, 123 (1959).

6. McCubbin, J. W., Kaneko, Y., and Page, I. H., Circul. Res. 11, 74 (1962).

7. Emerson, T. E., Jr., Scott, J. B., Daugherty, R. M., Jr., and Haddy, F. J., XXIV Internat. Congr. Physiol. Sci. 7, 125 (1968).

8. Texter, C. E., Jr., Chou, C. C., Merrill, S. L., Laureta, H. C., and Frohlich, E. D., J. Lab. Clin. Med. 64, 624 (1964).

9. Bohr, D. F., and Elliott, J., *Metabolismus Parietis Vasorum.* Comt. Rend. Congr. Intern. Angiol. 4th (1962).

10. Bohr, D. F., and Johansson, B., Circul. Res. 19, 593 (1966).

11. Iturri, S., and Emerson, T. E., Jr., Proc. Soc. Exp. Biol. Med. 137, 416 (1971).

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