2. Isoproterenol gives a depressor effect which tends to be reversed by propanolol. (Indicating presence of beta receptors.)
3. Hexamethonium (a ganglionic blocker) has no effect on blood pressure (presumptive evidence of absence of sympathetic vasoconstrictor tone), but DMPP (1-1 dimethyl-4-phenylpiperzinium), a ganglionic stimulator, caused a pressor effect which was blocked both by hexamethonium (ganglionic blockade) and by phentolamine (neuroeffector junction blockade).
4. DMPP stimulated parasympathetic ganglia resulting in depression of heart and gill movement rate. This effect was abolished by atropine. Otherwise, there was no evidence of autonomically mediated reflexes affecting heart or gill movement rates with the exception of an increase in heart rate caused by norepinephrine after phentolamine.

The drug experiments demonstrate that the dogfish has the capacity to respond to sympathetically active drugs in a fashion similar to mammals. The sympathetic ganglion-post-ganglionic, sympathetic neuron-neuro-effector structure appears to be developed. However, no evidence of operational sympathetic reflexes affecting the peripheral circulation (dorsal aortic system) could be observed. It is tentatively concluded that such reflexes have not yet developed in this primitive species.

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EFFECTS OF CATECHOLAMINES, SEROTONIN AND OTHER DRUGS ON GILL AND SYSTEMIC VASCULATURE OF S. acanthias

E. Converse Peirce II, Barbara B. Kent, Marjorie G. Peirce, and Carey G. Mumford III, Department of Surgery, Mount Sinai School of Medicine, New York, N. Y.

The actions of drugs in S. acanthias are of interest both from the standpoint of comparative pharmacology and of studies of the hypothermic state. Since it is often difficult to distinguish between cardiac and peripheral drug actions, even when cardiac output is known, there are distinct advantages in using a perfusion preparation. Where drugs are given in intact animals, changes in cardiac output, due to direct cardiac action or to baroreceptor reflexes, render interpretations difficult (Opdyke and Opdyke, Bull. MDIBL 9:44, 1969). The series arrangement of gill and systemic resistances in the dogfish makes it necessary to monitor both ventral and dorsal aortic pressures (VAP and DAP). The varying condition of the fish, the relatively prolonged effects of some drugs, the relatively large doses that are required, and the occurrence of tachyphylaxis, make it very difficult to obtain dose-effect curves in intact preparations. Another significant problem in the intact fish is the rather large changes that occur very rapidly after minor volume loading (Figure 1).

A perfusion preparation incorporating a membrane lung was described last year (Bull. MDIBL 9:45, 1969). Venous drainage is obtained from the left ventricle and blood is returned at a controlled rate into the ventral aorta. Drugs are injected into the ventral aorta instead of the dorsal aorta to insure distribution in the systemic circulation of the fish. The membrane lung was deleted from the studies this year because the gas exchange capability was not needed.

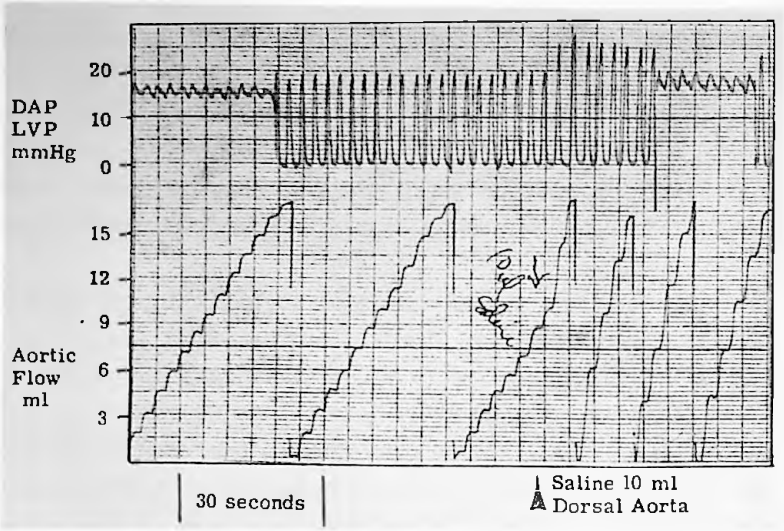

Figure 1.

The use of this perfusion preparation eliminated most of the problems of the intact fish.

Data obtained to date are summarized in the table. All drugs were given by slug injection in a volume of 1 ml into the VA cannula. Similar volume injections of saline did not produce a measurable change. For some drugs, single dose levels were studied, while for a few, dose-effect curves were obtained.

Table 1

Drug	Epi-nephrine	Norepi-nephrine	Dopamine	Isopro-terenol	Isopro-terenol after pro-pranolol	Serotonin	Serotonin after Atropine	Angio-tensin
Dose	4 γ/kg	4 γ/kg	64 γ/kg	16 γ/kg	4 γ/kg	32 γ/kg	128 γ/kg	100 γ/kg
VAP	↗	→	→	→	→	↗	→	→
DAP	↗	↗	→	→	→	↘	→	→
R_G	→	→	→	→	→	↑	↗	↗
R_S	↗	→	→	→	→	↘	→	→
R_T	↗	→	→	→	→	↗	→	→

1. Epinephrine: Blood pressure changes were obtained with doses of 0.25 γ/kg. The action was of long duration (Peirce, et al, Bull. MDIBL 7:40, 1969). Both DAP and VAP were increased and there was an increase in pulse pressure. Opdyke and Opdyke (Bull. MDIBL 9:41,44, 1969) noted these changes in lightly anesthetized fish and suggested that the vasoconstriction might be greater in the dorsal than in the ventral aortic system. Because of changes in pulse contour and heart rate they felt that the predominant effect was an increase in stroke volume and that the circulatory system of S. acanthias acted as a simple pressure-volume system,

little affected by vasomotor activity. The perfusion studies, in which there is no increase in available volume, clearly show that epinephrine increases systemic vascular resistance (R_S) and that gill resistance (R_G) is unchanged or slightly decreased at constant perfusion flow (Figure 2). The direct effect of epinephrine causing contraction of the smooth muscle of the gut

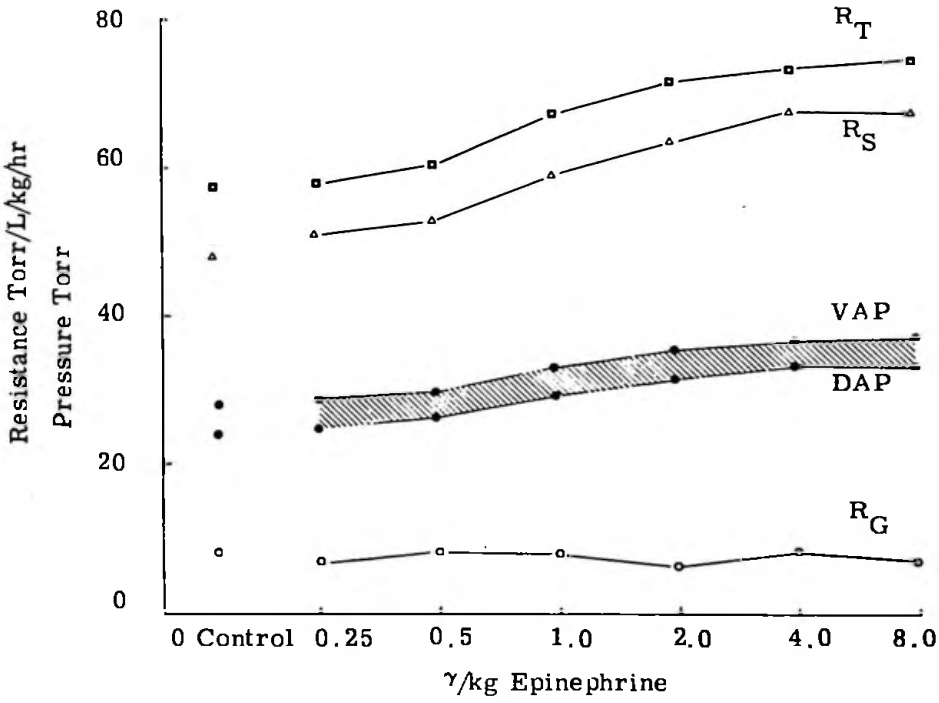

Figure 2.

could contribute to the increase in resistance as suggested by Diana and Diana (Bull. MDIBL 8:11, 1968). There was no evidence of tachyphylaxis with small doses of epinephrine. The duration of the effect after large doses was so prolonged that repeated doses, even after periods of 30 minutes or more, sometimes had no apparent effect. Regitine, 2.5 mg/kg, did not block the effect of epinephrine (one fish). This finding is in agreement with Burger and Bradley who found that dibenamine did not block the action of epinephrine (J. Cell. Comp. Physiol. 37:389, 1951) and Opdyke and Opdyke who found no blocking effect of phentolamine.

2. Norepinephrine: The effect was similar to that of epinephrine but the drug was less potent.

3. Dopamine: Slight decreases in both VAP and DAP occurred with doses of 16 to 256 γ/kg. R_G was not significantly changed while R_S was slightly decreased.

4. Angiotensin II: Response was very similar to that produced by epinephrine, as shown earlier by Peirce, et al (Bull. MDIBL 9:45, 1969). A dose of 250 γ produced an effect somewhat less than that of 10 γ of epinephrine and the duration of action was shorter.

5. Isoproterenol: Small decreases in both R_G and R_S occurred. We had previously found the effect difficult to detect in a nonperfused preparation. Opdyke and Opdyke reported larger, but otherwise similar, changes. After propranolol, both R_G and total resistance (R_T) were very strikingly increased and further administration of isoproterenol increased these elevated resis-

tances (Figure 3). A reversal of the isoproterenol effect on blood pressure was reported earli by Opdyke and Opdyke. One plausible explanation would be that isoproterenol has both vasocon strictor and vasodilator effects and that the vasodilator effect is blocked by propranolol.

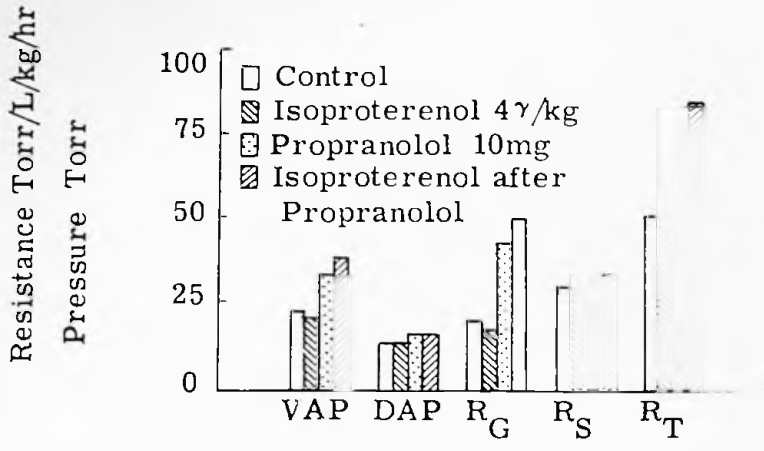

Figure 3.

6. Serotonin (4-hydroxytryptamine): Serotonin produced an unusual response with a very marked increase in R_G and a decrease in R_S (Figure 4). Drug action was of relatively long dur tion. There was no evidence of tachyphylaxis with small doses. The action of serotonin was not blocked by atropine (in a dose greater than 12 mg/kg) though there was diminution in the response (Figure 5). In nonperfused fish there was a very marked bradycardia and decrease in t rate of gill movement (Figure 6).

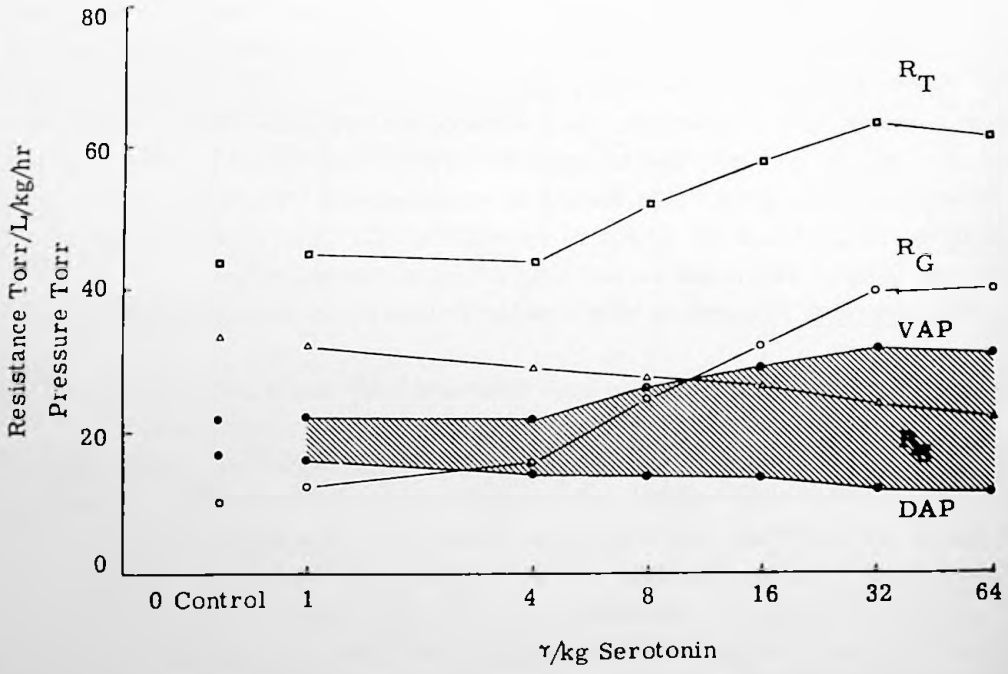

Figure 4.

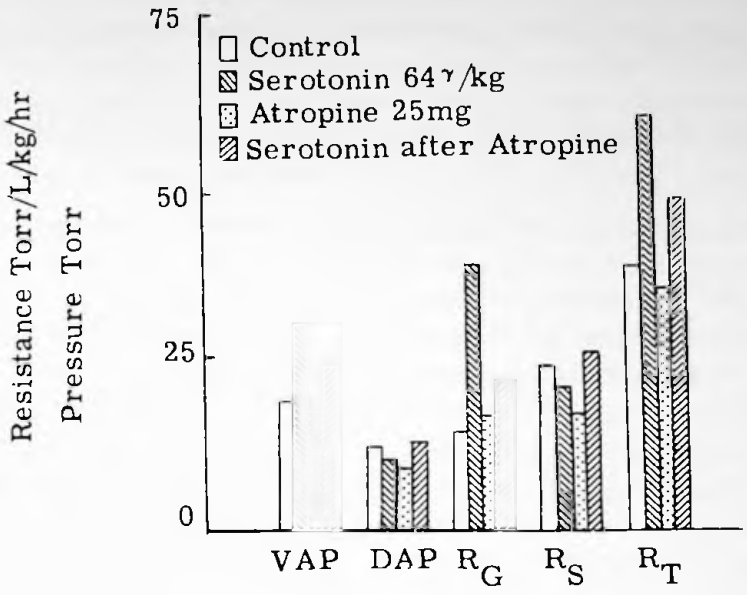

Figure 5.

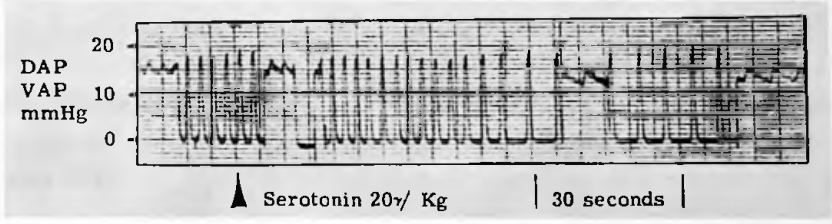

Figure 6.

The response to serotonin is of particular interest because this material may be the neuromuscular transmitter substance in some invertebrates and because the pattern produced by its administration is similar to that seen in hypoxia and hypercapnia in the dogfish (Kent, et al, Bull. MDIBL 8:35, 1968 and 9:18, 1969; Peirce, et al, Bull. MDIBL 9:45, 1969). The response to hypoxia and hypercapnia was found to be blocked by either vagotomy or the administration of 2 mg/kg of atropine sulphate IA. This pattern has been seen under only two other circumstances. In one instance blood from a very hypoxic donor was used in the perfusion circuit (Peirce, et al, Bull. MDIBL 9:45, 1969). In the second, a very similar pattern was seen with the administration of the prostaglandins E_1 and A_1. The data suggest that although the response to hypoxia and hypercapnia is almost certainly the result of a vagal reflex, release of a serotonin-like material may play a part.

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