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Conclusion: Comparative physiology of cardiovascular control

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The symposium on which this multi-author review is based covered a series of related topics centered on neural and neurohumoral control of cardiac output, neural control of the myocardium and circulatory system, and central neural visceral regulation.

Cardiac output

P.J.S. Smith has addressed a fundamental difference in regulation of cardiac performance during a period of increase in tissue demand for delivery of oxygen ('exercise'). The systemic heart of the octopus, unlike the systemic heart of mammals, responds to exercise with increased stroke volume, but no substantial increase in heart rate. This difference is taken as the basis for an enquiry into the underlying cardiovascular control mechanisms in the Mollusca, based on experimental work with the isolated entire heart of *Busycon canaliculatum*. In this preparation both stroke volume and heart rate respond to changes in input perfusion pressure, but significant changes in stroke volume require changes in venous return pressure which seem unlikely in the open cardiovascular system of prosobranch gastropods. This observation led to a consideration of the role of extrinsic factors in

cardiac regulation, such as cardioactive substances which may be released into the circulation, or released from nerve endings to act as local hormones. Such an approach offers the advantage of correlating the extrinsic control of the output of *B. canaliculatum* heart (in vitro), with neural regulation of the *B. canaliculatum* ventricle, which was previously reviewed[4]. The results indicate that (in vivo) 5HT (5-hydroxytryptamine; serotonin; enteramine) may regulate flow rate and pressure, as compensation for increased peripheral resistance. Certainly, in vitro 5HT induces the ejection of a fixed stroke volume at a greater pulse pressure, at increased flow rate.

In the intact animal, quick ejection may be induced by repetitive activity in the cardiac nerve, which induces rapidly depolarizing fused EJPs[4].

Low concentrations of a tetrapeptide, FMRFamide, which may sometimes act as a long-acting serotonergic mimic, are shown by Smith to act like 5HT on the heart of *B. canaliculatum*. This suggests that future studies could profitably be directed toward discovering whether circulating neuropeptides may support longlasting forceful cardiac output against increased peripheral resistance.

ACh (acetylcholine) may regulate heartrate, strength of pressure pulse, and stroke volume in the heart of *B. canaliculatum*. The review by P.J.S. Smith indicates that perfusion of the heart in vitro with ACh reduces all three factors: heart rate, stroke volume, and amplitude of pressure pulse. In the intact animal these factors may be controlled by a 'vagal tone' in the cardiac nerve, which induces summating, hyperpolarizing, fused compound IJPs[4]. Both excitatory serotonergic tone and inhibitory cholinergic tone may be modulated in response to afferent stretch receptor activity in the cardiac nerve of *Busycon canaliculatum*[4] which reflexly induces afferent activity in the cardiac nerve[5]. Results reviewed by Smith indicate that in both *B. canaliculatum* and *A. californica* cholinergic control may interact with returning venous pressure to allow a larger end-diastolic volume, in the relaxed heart, for the same venous filling pressure. This in itself might lead to a larger stroke volume, by a Starling's Law mechanism, and interplay with aminergic control could lead to rapid ejection of the increased stroke volume.

A number of observations, reviewed by Smith, indicate that circulating FMRFamide, 5HT or unidentified bloodborne factors may induce transformation of the electromyogram of an entire opisthobranch ventricle, from a simple waveform to a more complex spike and plateau action potential, with an accompanying increase in force of contraction or an increased pressure pulse in the cardiac output.

Visceral regulation (Pulmonata)

Dr K.S.-Rósza has addressed visceral regulation in *Helix pomatia*, comparable in many ways to autonomic visceral regulation in Vertebrata. A network of coupled identifiable neurons in the subesophageal ganglion receives afferent peripheral information and acts in a temporary combination of regulatory units, which can substitute for each other in regulation of cardio-renal, respiratory, or genital functions.

Dr S.-Rósza's data provide an alternate approach to the interpretation of functional networks, for visceral regulation, in the molluscan central nervous system. The command neuron or fixed-action-pattern approach may require that individual units or networks are evolved to serve a single function. Her data indicate that a given unit or network may instead serve alternating roles, as overlapping neural populations form dynamic combinations, depending on the demands of the moment. Her emphasis on interaction of neurotransmitters in an identified neural network extend the concept of interaction of neurotransmitters, seen at a peripheral cardiac output level in Dr. Smith's contribution. Peptides like FMRFamide act on a network of identifiable neurons, in the subesophageal ganglia of *Helix pomatia*, both to modulate the action of classical neurons and to block habituation.

Neural control (Opisthobranchia)

Koester and Koch review neural control of the cardiovascular system of *Aplysia californica*. They emphasize that megacell neurobiology offers the opportunity of understanding control of circulatory function as an element in neural control of behavior in *A. californica*. Identified abdominal ganglion neurons which innervate the heart may release neurotransmitters or neurosecretory products such as serotonin (RB_{HE}) or acetylcholine (LD_{HI}), but identification of neurotransmitters controlling the heart remains in the future for such important cardiovascular motoneurons as LD_{HE} and L_7. It seems particularly interesting that the heart of *A. californica* receives terminals from the neurosecretory neurons R_7 and R_8, which form part of a cluster of cells, secreting neuropeptides and probably also releasing glycine as a neurotransmitter.

Understanding of the cardiovascular system in *A. californica* has progressed beyond the studies of the heart, which are common for other gastropods, to identification of eight classes of neurons modulating vascular muscle. Of these vaso-modulatory neurons, the LB_{VC} cluster is cholinergic and L_7 is synergistic with the LB_{VC} cluster when they are caused to fire together experimentally. R_{14} is a neurosecretory cell, which may also release glycine as a neurotransmitter for vascular muscle. Heart rate responses of *A. californica* to food stimuli and to respiratory pumping are under direct neural control, as are spontaneous increases in heart rate. Such increases in heart rate are generated by endogenous bursts of action potentials in L_{10}, which cause an increase in heart rate by exciting RB_{HE} and inhibiting both LD_{HI} and the peptide-containing clusters of cells, L_2–L_6, in 'semi-intact' preparations.

During feeding by *A. californica*, heart rate increases in synchronization with blood pressure and blood flow in the anterior aorta. A beginning has been made in identifying the central neuronal mechanisms underlying these cardiovascular correlates of feeding. For instance, the firing rate of RB_{HE} increases by 50% in the 'semi-intact' preparations, while cutting the cardiac axon of RB_{HE} eliminates $\frac{2}{3}$ of the heart rate increase in the intact animal. An important aspect for future study is the coordination of somatic motor control with phasic visceral motor control, as is seen in the coordination of biting activity with the cardiovascular correlates of feeding.

In general, Koester and Koch point out, rapid phasic vasomotor effects are generated by cholinergic neurones, in which ACh acts as a direct neurotransmitter, while tonic modulation is mediated by serotonergic cells.

A behavioral act, in which involvement of the cardiovascular control network is particularly well understood, is that of respiratory pumping in *A. californica*. Contraction of the gill is accompanied by relaxation of the heart, so that blood from the gill fills the heart, and is then forced out to the circulation. The multi-neuronal network of interneurons driving respiratory pumping may function in temporary subsets, rather as proposed by S.-Rósza for *Helix pomatia*.

Neural control (Prosobranchia)

Kobayashi reviews the innervation and control of the heart of a prosobranch gastropod, *Rapana thomasiana*, in a preparation in which the roles of neurotransmitters and neuropeptides may profitably be compared to the roles seen in opisthobranchs and pulmonates. In the case of *R. thomasiana*, ACh is the inhibitory neurotransmitter while 5HT seems to be an excitatory local neurohormone. FMRFamide is serotonin-mimetic, but is not blocked by serotonin blockers.

Four cardiac nerves which innervate the atrium contain predominantly excitatory axons, while two cardiac nerves which innervate the ventricle contain predominantly inhibitory fibers. Acetylcholine inhibits the heart of *R. thomasiana,* and benzoquinonium (Mytolon) or propantheline block both ACh inhibition, and the effects of the inhibitory cardiac nerves. Serotonin (5HT) excites the heart of *R. thomasiana* and methysergide blocks both 5HT excitation, and excitation induced in the denervated heart after stimulation of the circumesophageal ganglia. These results suggest that ACh is a direct inhibitory neurotransmitter, but that serotonin may be released as a neurohormone by axons from the circumesophageal ganglia. Methysergide does not block the effects of the excitatory cardiac nerves.

The cardiovascular system of *R. thomasiana* offers an interesting opportunity to compare the effects of 5HT and FMRFamide. In general, the bioactive amine (5HT) and the neuropeptide (FMRFamide) have similar cardioexcitatory effects. However, the concentration-action curve for FMRF amide is shifted to the left from that for 5HT: lower threshold, and greater action at each concentration, with regard to force of heartbeat. With regard to rate of heartbeat, 5HT is consistently strongly excitatory, but FMRFamide is regulatory, tending to hold frequency in a moderate range. FMRFamide itself may be a physiological regulator, since it is the most potent of 14 peptides tested.

Mechanism of inhibitory control (Opisthobranchia)

Kuwasawa and his colleagues have reviewed control of opisthobranch myocardium by transmitters released at neuromuscular junctions, mainly in *Dolabella auricularia* and *Pleurobranchaea novaezealandiae.* In these forms, ACh pulses elicit Na-sensitive depolarizing (D) responses in ventricular muscle, and chloride-sensitive hyperpolarizing (H) responses in muscle of the AV valve. Both the H-responses to ACh, and IJPs elicited by stimulation of the cardiac nerve, are inverted into depolarizing responses in the absence of chloride.

This is of interest with regard to the mechanism of action of ACh in its role as an inhibitory neurotransmitter[3]. Both depolarizing responses and hyperpolarizing responses had previously been attributed to decrease in membrane resistance[3], but were presumably mediated by different ionic currents. In the present review by Kuwasawa and his colleagues, it is pointed out that the D and H-responses to acetylcholine are differentially sensitive to cholinergic antagonists in ventricle and AV valve of *D. auricularia* and *P. novaezealandiae.* This offers the possibility of classification of differential effects of ACh on ionic currents in several target tissues, including both neurons and muscle cells. In *D. auricularia* and *P. novaezealandiae,* ACh has a sodium-dependent depolarizing effect on ventricular muscle, which is blocked by hexamethonium and may thus resemble similar responses of bivalve hearts, (reviewed by Kuwasawa et al. above) and a chloride-sensitive hyperpolarizing effect on AV valve muscle, which is blocked by tubocurarine, as are chloride-sensitive IJPs. Thus it appears likely that cardiac inhibition in these species is mediated by a cholinergic increase in G_{Cl}. However, the role of the cholinergic depolarization, mediated by an increase in G_{Na}, is still uncertain.

Discussion

The control mechanisms reviewed here range from the effects of stretch, through post-junctional responses to neurotransmitters and tissue responses to circulating neuroactive agents, to neuronal control mechanisms in gastropod ganglia. In the future it may be necessary to extend the hierarchy of ganglionic control mechanisms, as was foreseen by Lacaze-Duthiers in 1898[6]. Lacaze-Duthiers pointed out that the cerebral ganglia should dominate, since they are in direct communication with all the other centers, except that the three 'splanchnic' ganglia interposed between the two pleural ganglia may 'report' through the intermediate pallial center (the pleural ganglia). This is at least in accordance with the hierarchy of afferent pathways in the innervation of the heart of *B. canaliculatum*[5].

Smith has suggested the hypothesis of a humorogenic heart, supported by the level of circulating peptides. This is supported by Kobayashi's observation that FMRFamide is regulatory; positively chronotropic in a slowly beating heart, but negatively chronotropic in a rapidly beating heart. In the case of Smith's observations on working hearts of *Aplysia dactylomela,* perfusion with blood rather than with saline (seawater) enhances performance of the isolated heart and tends to convert the electromyogram from a simple type to a complex spike-and-plateau type. Factors may circulate in the blood, with actions like those of 5HT[12] and FMRFamide[13].

A species closely related to *A. dactylomela* is *Dolabella auricularia,* for which a series of studies link the possible humorogenic effects on the in vitro working heart to humoral actions on myocardial cells. Matsui[7,8] has shown positive effects of increased external load or internal pressure on the isolated ventricle of *D. auricularia.* Nomura[9] showed that stretching increases both the rate of rise of the prepotential and the duration of the action potential in ventricular muscle fibers of *D. auricularia,* and that plateau duration is linearly related to force of contraction. The relation of force of contraction to the duration of the plateau of the cardiac action potential has also been studied in whole ventricles of *Dolabella auricularia*[1]. Preliminary results are now available from a new series of experiments with *D. auricularia* in which treatment with 5HT was used to quantify the relationship between form of the plateau phase and force of contraction, in ventricles which were quiescent when not treated with serotonin. The lowest force of beating, at 10^{-8} M 5HT, corresponds to slow simple action potentials. As 5HT concentrations are increased from 10^{-7} M to 10^{-6} M (fig. 1), action potentials become differentiated (showing prepotential, spike, and plateau phases) and force of beating increases markedly. Another stage of increased force is elicited by 4×10^{-6} M 5HT (fig. 2). The spike phase remains relatively fixed in amplitude and time course, but is more or less obscured as the plateau phase waxes and wanes. Force is closely

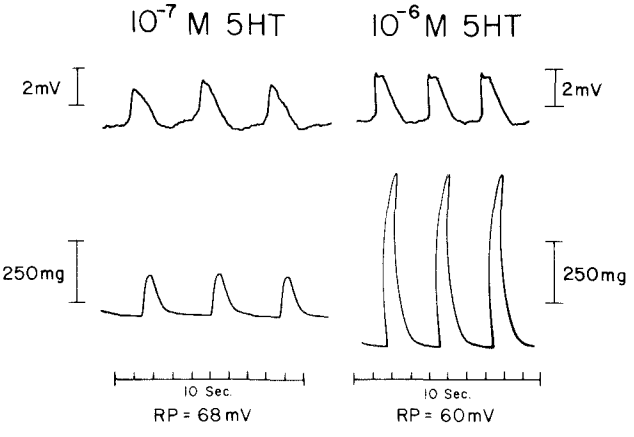

Figure 1. A chart recording showing a relation between form of ventricular action potentials and myocardial force, in the heart of *Dolabella auricularia.* In this and subsequent chart recordings, the upper record is potential difference across a sucrose gap, while the lower record is auxotonic force in a compartment perfused with filtered seawater (FSW). In a low concentration of serotonin creatinine sulfate (10^{-7} M 5HT) the action potential was relatively undifferentiated. In a higher concentration (10^{-6} M 5HT), a more differentiated action potential was accompanied by enhanced ventricular force.

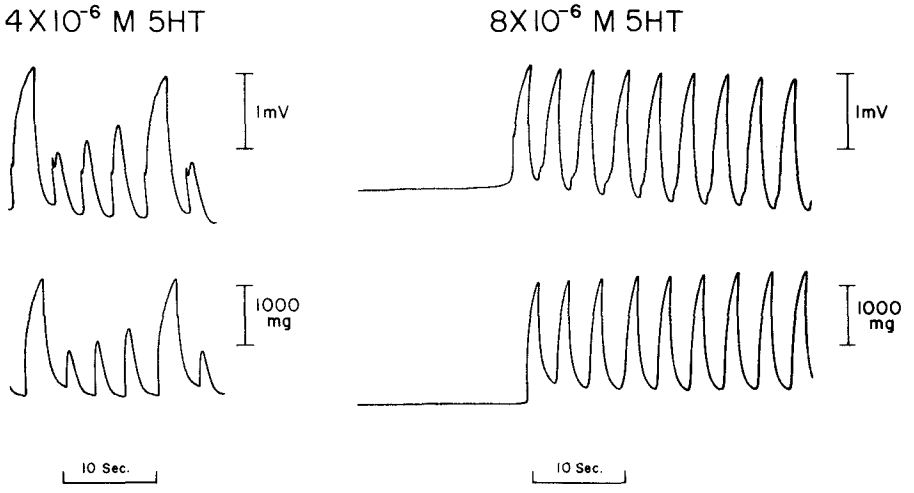

Figure 2. Under the influence of high concentrations of serotonin, force mirrors plateau amplitude in ventricular myocardium of *D. auricularia*. (These records form a sequence, with those in fig. 1). At 4×10^{-6} M 5HT (left) maximum force is greater than at 10^{-6} M 5HT, and is related to plateau amplitude while spike amplitude remains almost unchanged. At 8×10^{-6} M 5HT (right) a preparation begins to beat with a relatively large spike amplitude, which quickly diminishes. However, both plateau amplitude and force remain relatively fixed at a high amplitude.

correlated with the amplitude of the plateau phase, which may be several times the height of the spike. Finally, at 8×10^{-6} M 5HT amplitude of the plateau phase has increased to a maximum at which the spike can hardly be distinguished and there is no prepotential. At this stage, the plateau has taken on the appearance of a smooth wave several times larger than the small slow action potentials which accompany the smallest beats. These maximal action potentials, which accompany steeply increased force, resemble cardiac action potentials of *Aplysia californica*[1]. Aplysiid myocardium thus may function much like myocardium of *Busycon canaliculatum*. In isolated working hearts of *B. canaliculatum*, stroke volume increases with preload in parallel with increased differentiation of the plateau phase of the suction electrogram from the ventricle[11]. However, aortic pulse pressure also increases markedly in parallel with the differentiation and increased amplitude of the plateau phase induced by 5HT[12] or FMRFamide[13]. It is thus likely that stretch, release of neurohumoral transmitters, and circulating peptides[10] may all interact to support demands for increased cardiac function, a concept for which support may be drawn from the reviews gathered together here.

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