Cardiac Memory and Cortical Memory

Do Learning Patterns in Neural Networks Impact on Cardiac Arrhythmias?

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Abstract*—**Memory is a property of diverse biological systems, including brain and heart. Studies in cortical neuronal networks have identified an increased sensitivity to infrequent (rare) stimulation patterns that can result in their achieving dominance over network firing. This adaptive behavior is applied to the heart in an attempt to explain the ability of pulmonary venous and other ectopic foci to achieve dominance over cardiac rhythm. Developmental changes in determinants of cardiac rhythm are explored as possible determinants of the range of rhythms expressed by the heart. By understanding the mechanisms for these behavior patterns, we may obtain new means for manipulating memory to return dysrhythmic hearts to normal sinus rhythm. (Circulation*. 2003;108:1784-1789.)**

Key Words: tachyarrhythmia ■ nervous system ■ atrium ■ heart rate

The statement "atrial fibrillation begets atrial fibrillation"[1] suggests that expression of this cardiac arrhythmia results in evolution of an environment favoring the further occurrence of the arrhythmia. The corollary, "sinus rhythm begets sinus rhythm," has been less well tested. Rather, the general picture is of arrhythmias interrupting sinus rhythm and evolving more or less inexorably. In instances in which individuals experience arrhythmias for self-limited periods, the usual assumption is that whatever substrate and/or triggering event that favored the arrhythmia is no longer present. These statements regarding arrhythmia mechanism derive from a mind-set that considers cardiac cells to be ordered machines that periodically resynthesize their component parts in either a normal or abnormal pattern on the basis of their genetic map and the influence of environment. In this context, arrhythmias represent the intrusion of unexpected and novel forms of electrical activity interposed on normal cardiac function. We stress the words "unexpected" and "novel" because the preconception is that rhythms other than sinus are foreign to the circumscribed universe of normal cardiac function. We now suggest that rather than being novel and unexpected, arrhythmias represent the downstream expression of electrical activity native to the heart, albeit activity previously limited in expression.

This suggestion evolves from recent research on cardiac memory and on the biophysics of activation path formation in neural networks. In exploring potential linkages between neural and cardiac systems, we shall consider memory as the retention of an acquired (learned) signal. In neuronal networks, the result of this signal is expression of an activation path whose physiological manifestation is a particular pattern of firing.[2,3] In heart, the result of this signal is most often described as an altered T wave on the ECG such that its vector follows that of the QRS complex of a previously paced (or arrhythmic) beat or beats.[4]

The following discussion will (1) consider general principles underlying the appearance and stabilization of activation paths in neural networks, emphasizing how rarely expressed events can become dominant; (2) review related behaviors of myocytes in the developing heart with the aim of exploring why rare events can become dominant and devastating; and (3) synthesize both sources of information to develop the hypothesis that arrhythmias represent the uncovering of concomitant, albeit rarely expressed, patterns of activity. It is our hope that by exploring why the heart might be so sensitive to rare activations from alternative foci, we will begin to obtain new insights into arrhythmogenic mechanisms and modalities for prevention and therapy.

Lessons From Neuronal Networks

This section reviews some neurophysiological observations that may be relevant to cardiac memory. We start with the concept of an activation map composed of paths through which electrical signals travel and which is common to both cardiology and neuroscience. As an example, we use the cortical sensory representational map,[5] a topographical arrangement of neurons characterized by correlation with the topographical arrangement of the sensory envelope of the body. Although at one level their component parts are genetically programmed, cortical maps are themselves the outcome of activity throughout development. Both in cortex and in cardiac muscle, such maps are specific and dynamic,

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with the potential to change throughout life as their correlation with related physiological functions changes: movement and sensation for cortical maps, contraction and electrical throughput for cardiac maps.

The signals that activate a given sensory map area originate from well-defined foci on the body surface, the cardiac parallel being primary or secondary (or artificial) pacemakers from well-defined foci. Three corresponding cortical issues seem relevant to our discussion of the heart, two of which will be discussed here and the third mentioned at the end of the article:

(1) the mechanisms underlying the formation and expression of neuronal maps,
(2) the relations between insults to an activation source (sensory foci in the body surface) and the nature of change in the representative map, and
(3) the kinds of measures that can be taken to rehabilitate a loss of function caused by a damaged map area.

With regard to the first issue, an idea that has captured the imaginations of neuroscientists for more than a century is "association by simultaneity." From Freud[6] and James[7] toward the end of the 19th century, through Hebb's seminal work on the psychobiology of association in the mid-20th century,[8] to the flood of modern articles on neural plasticity (reviewed in Reference 5), a common insight is shared: Neural entities that are activated together tend to form a structural infrastructure for communication among themselves. The slogan "fire together, wire together" captures the essence of the idea. In fact, it has been clearly demonstrated that representational maps naturally emerge when such an association-by-simultaneity rule is applied. Thus, if we are to relate neural to cardiac events, the cardiac correlate of this concept is important.

The second issue is that the maps are dynamic, on many scales. As an input from the sensory sheath changes (a person learns to play the piano), the structure of the map is altered. When such input changes occur, alternative maps intervene and appear always related in some form to the dominant ones. Thus, if a finger is cut accidentally, fields controlling related skin areas intervene.[5] In that respect, it is tempting to consider the uncovering of developmental evolution and competition when a map is "insulted." We can extrapolate this information to ask how similar competition between alternative yet related maps might translate to alternative yet related cardiac activation paths under conditions of cardiac insult. For instance, do the paths traveled during development determine the potential array of "aberrant" paths that might appear in the future; are we, by observing those aberrant paths, "reconstructing" the past time of a heart?

A related issue is the nature of "elastic" responses to varying sources of activation. Most relevant in that context is the tendency of the brain to enhance its sensitivity to rarely occurring events.[9] This property has potential value because the rare event contains information that may matter for survival. Recently neurophysiological correlates to this phenomenon have been observed in brain imaging,[10–12] electroencephalography,[9,13] and intracranial single neuron recordings.[14–16] Importantly, cell-physiological studies have suggested that sensitivity to the rare is not a property of single neurons but rather a network phenomenon.[9,14,16–18] Given the ubiquitous nature of sensitivity to the rare in perception, it is reasonable to assume the existence of a general underlying neurological mechanism. Indeed, it has been suggested that responsiveness to rare stimuli imposed on the background of other frequent input(s) does not represent a de novo path; rather, it is the expression of an existing path that is regularly suppressed by more dominant ones (D. Eytan, N. Bremer, S. Marom, preliminary data). The repetitive activation of the dominant paths causes stimulus-specific adaptation via mechanisms of path inactivation and interaction with other, dormant paths. Moreover, enhanced sensitivity to rare sources of activation requires that there be some (but never complete) overlap between existing activation paths of the frequent and the rare. In this context, the source of activation that elicits the greatest response is rarely active when considered in relation to another, more frequently firing source.

Projecting these observations from neural networks to their cardiac implications, bursts of activity of pulmonary venous foci might be considered rare with respect to the long-standing presence of a dominant sinus rhythm. That such activity ultimately can invade and dominate both atria, translating sinus rhythm to atrial fibrillation might be a cardiac example of sensitivity to the rare. Hence, under the assumption of some universality in the behavior of excitable networks of cells, and using information of the kind mentioned above to associate neural and cardiac memory, we propose the following.

(1) For activation and repolarization paths to be formed, some synchronous activations and repolarizations of their elements must have occurred previously (a restatement of Hebb's law).
(2) As in neural maps, there are many potentially expressible paths, but only a subset dominate(s) ongoing activity. Furthermore, on the basis of neurophysiological insights, we propose that the dominance of a path does not abolish the ability of the less dominant path to be expressed; rather, the results from studies on sensitivity to the rare suggest that the dominant path plays a role in enhancing the response of rarely evoked paths.
(3) As in neuronal systems, activation paths become dominant using elementary processes such as activity-dependent attenuation of conductances.
(4) Dominant paths are structured hierarchically such that competition among their elements plays a role in determining which will appear in the subsequent beat.
(5) Appearance, on the basis of the same activity-dependent processes as described above, determines the probability for future path appearance.
(6) It is highly improbable for a path to be expressed that is not supported by underlying functional, anatomic, and molecular structure.
(7) The paths taken during development may well determine the possible array of aberrant paths that might appear in the future; we therefore might speculate that observation of those aberrant paths may facilitate reconstruction of the past.

Development, Learning, and Memory in Heart

In making the leap from neuron to heart, we are working across systems that at first glance appear discordant, as follows: Neurons contact one another via synapses such that information is transmitted at a relatively long distance from the cell body. In contrast, myocytes contact one another via gap junctions that are integral parts of a quasi-rectangular cell and that operate over short distances. Moreover, synaptic physiology is such that in response to a rare event, transmitter release is elevated, or at least remains fixed, whereas in response to a frequent event, release is depressed, an adaptation characteristic of the plasticity of neural networks.[17,19] That such an adaptive function may exist in heart and be applicable to both physiology and pathology may seem counterintuitive. We now explore whether—counterintuitive or not—the possibility is worth exploring. The discussion is based on the following premises: (1) The developing heart as well as ventricular myocytes in cell culture are driven by a pacemaker or pacemakers, one of which over time will tend to become dominant; (2) cardiac activation patterns will be determined by the site of impulse initiation, by the basic roadmap of specialized conducting fibers, and by the mechanical demands placed on the heart; (3) whereas synapses provide a major source of cell-to-cell communication among neurons, gap junctions serve a similar function in heart; and (4) there is activity dependence of connections (whether synapses or gap junctions) and of overlapped hierarchical paths.

Development

In the heart, in situ pacemaker activity commences in the 6 to 7 somite stages of development in chick embryos and the 3-somite stage in rat.[20] Hence, the genetic programming of the heart is such that despite the potential of myocytes to manifest various types of activity, only one form of activity and one path of activation and repolarization becomes dominant during development.

The evolution of cardiac activation paths also can be considered from the perspective of the elementary cardiac myocyte, the embryonic stem cell. This manifests multiple electrical activities, including automaticity, early and delayed afterdepolarizations, and either rapidly or slowly rising action potentials of the sort that would permit, respectively, rapid or slow conduction in the functional syncytium that is the heart.[21] Fetal or neonatal myocytes plated randomly in culture demonstrate spontaneous activity that may be bursting or regularly rhythmic.[22] Their activity pattern may be such that different regions of one culture show different rhythms and rates or that uniformity of initiation and propagation occurs. Hence, it is possible in cultured myocyte systems to see ordered and uniform activity or a variety of nonuniformities.

Developmental changes in electrophysiological activity of myocytes result from at least two primary processes: (1) the function of ion channels, pumps, and exchangers to generate currents determining the action potential and (2) the connectedness of cells permitting ordered conduction to proceed. Yet both the determinants of cell-to-cell communication and those of the action potentials undergo developmental change. For example, the major protein subunit determinant of cell-to-cell communication in adult ventricle is connexin43, but in embryonic mouse heart just beginning to contract, connexin45 is the major subunit determining such communication.[23]

Similarly, developmental changes occur in ion channels that determine both impulse initiation and repolarization. With respect to impulse initiation, the pacemaker current, I_f, is demonstrable in rat neonatal ventricular myocardium, in which it activates in a physiological range of potentials.[24] Yet with postnatal development, those tissues outside the sinus node see I_f activation occurring at ever-more-negative potentials,[25] leaving the sinus node as the primary site of pacemaker activity. Because ventricular muscle still has I_f,[25] under the appropriate conditions it may again initiate spontaneous activity.[26] With regard to repolarizing currents, the transient outward current, I_{to}, is not demonstrable in neonatal rat or canine heart and in both species appears at about the time of sympathetic innervation,[27,28] whereas the delayed rectifier current sees its rapidly activating component large in the fetus and diminishing with postnatal age[29] and its slowly activating component absent to small in the fetus and increasing with postnatal age.[30] These and other changes in ion channels bear witness to the developmental plasticity of the heart.

A third aspect in our consideration of changes in myocardium as a result of altered activation is the role of altered stress/strain relationships. A major factor here is angiotensin II, whose synthesis and release in heart increase in response to altered stress/strain.[31,32] In tissue culture, angiotensin II synthesis and release occur in fibroblasts and/or myocytes.[33] Angiotensin II is a potent modulator of ion channel function and of myocardial hypertrophy,[34] acutely altering the function of $I_{Ca,L}$[35] and, on chronic exposure, I_{to},[36] and affecting myocardial structure and function as well.[37,38] A postnatal decrease in angiotensin II receptor number also has been demonstrated.[37,38] Given the dual roles of angiotensin II as ion channel modulator and potent hypertrophic stimulus, it is likely that in the hours to days after birth, it is a major determinant of the ion channel changes and the physiological hypertrophy that occur. However, its important regulatory effects are not limited to the newborn. For example, adult canine ventricular epicardial myocytes manifest a reduced phase 1 notch and I_{to} and prolonged action potential duration on several hours' exposure to angiotensin II.[36]

Learning and Memory

The point to be driven home via the examples cited above is that genetic and humoral control mechanisms determining both anatomic structure and pathways underlie the events that initiate, activate, and repolarize the myocardium. What, then, does this information about development have to do with learning and memory? As an initial template, we propose that the developmental evolution of a primary pacemaker locus and an ordered anatomic path for activation set the conditions that determine the expression of impulse initiation, propagation, and repolarization in the adult. In other words, cardiac activation and repolarization as recorded electrocardiographically represent the net response of the totality of cardiac myocytes to a single, repetitive stimulus (the sinus node action potential) following the same pathway and are seen as

the normal P wave, QRS complex, and T wave that characterize sinus rhythm.

The cardiac memory that follows the occurrence of ventricular pacing, ventricular arrhythmia, preexcitation, or intermittent bundle-branch block results from the imposition of a stimulus and activation path different from those of sinus rhythm on the heart. Although this can provide the dominant source of impulse initiation and myocardial activation over a variable period of time, from the point of view of the prior history of accrued heartbeats, it represents a rare event. Yet this rare event recurring over the course of minutes to hours has an influence analogous to that of a rare event in a neuronal network. As the rare event recurs in myocardium, it can generate changes in gap junctional pattern density and distribution[39] as well as changes in repolarization seen at the level of the ion channel, the ion current, the action potential, and the T wave.[40–42] As changes in gap junctional patterns emerge, is there partial inactivation of the formerly frequently activated path (determined by sinus rhythm) and increased expression of the rarely activated path? If so, then the basis for the rare event achieving dominance can increasingly be appreciated.

Moreover, rare cardiac events may not necessarily form new paths but rather may become more effective in driving the system because of partial inactivation of the frequent paths. In this respect, the activation paths of rarely occurring sources uncover earlier stages of development. If rare events recur frequently, then Hebb-like rules[8] would make them ever stronger, even dominant. It logically follows that other "rare" paths may then challenge the newly dominant, as in the case of pacing paradigms used to suppress/terminate arrhythmias.

The changes that occur after altered activation of the heart are associated with alterations in the underlying molecular determinants of the ion channels and gap junctions, and very importantly, they largely represent a return to an earlier stage of development. For example, in fetal heart and in neonatal myocytes in situ or in tissue culture, connexin43 staining reveals a disordered pattern of gap junctional proteins, with both end-to-end (longitudinal) and side-to-side (transverse) staining of the myocytes.[43–45] During development, gap junctional rearrangement occurs, such that in mature ventricular myocytes, gap junctions are essentially concentrated longitudinally, following the long axes of the fibers. This orientation facilitates longitudinal rather than transverse propagation. When the mature ventricle is paced for days to weeks, altering the ventricular activation pathway, gap junctions are reoriented along the lateral margins of the cells, a distribution resembling the fetal pattern. Similar gap junctional reorientation occurs with other stresses as well (eg, myocardial infarction).[46,47]

The transient outward current, I_{to}, that determines the action potential notch and is in large part responsible for the transmural repolarization gradient in ventricle also is altered in response to ventricular pacing.[41] The resultant cardiac memory incorporates a decrease in the action potential notch, an altered transmural repolarization gradient, prolongation of epicardial action potentials, a decrease in the density of and altered kinetics of I_{to}, and a reduction in message for Kv4.3, the gene product responsible for the α-subunit of the channel. These changes, like those in gap junctions described above, represent a return to an earlier or fetal pattern in which no I_{to} is manifested.[27,28]

In a very real sense, then, the phenomenon of cardiac memory, as classically defined on the ECG,[4] can be interpreted not only as a process of "learning" but also as a process of "recalling" a previous pattern. In this context, cardiac memory would be based on electrical and ionic activities that were dominant in the earlier evolution of the heart and then relegated to the background during normal maturation. These activities, which may be thought of as rare in comparison to dominant cardiac activity, are brought again to the fore. One might consider this a return of entropy, ie, to a less ordered, immature state. This leads us to ask whether the normal adult pattern might require continuous reinforcement for its maintenance.

Formulating a Hypothesis

Thus far, everything we have stated is based on scientific observation blended with speculation. Our intent now is to present an hypothesis that, although based on existing knowledge, deviates from orthodox thought regarding arrhythmias. This formulation is based on acceptance of the following observations made on networks of cortical neurons in vivo as well as in tissue culture.

(1) Neurons are motionless: Their behavior is not modulated by changing stress/strain relationships among cells in a network. This rather obvious statement is made to highlight the complexity deriving from the mechanoelectrical interactions of the heart.
(2) Neurons in culture manifest spontaneous activity, having dominant rhythms and those that are rare, and whose frequencies have been recorded extensively. (For review, see Reference 3.)
(3) Lesion experiments in vivo as well as learning experiments in vitro suggest that newly formed paths/maps have some relation to existing paths/maps.[2,5]
(4) In the setting of a dominant activity, a neuron responds with far greater sensitivity to a rare than to a dominant event. The net result is that what once was rare, if repeatedly activated, can come to predominate and vice versa.

We now hypothesize that any arrhythmia that occurs in an otherwise normal heart does so because it is predetermined by activity previously expressed and/or latent (but in either event, rare) in that heart. In effect, no arrhythmia would represent a new event but rather the enhanced expression of that which is present already. Moreover, an effective therapy would be one acting at a level to recall the dominant electrical activity that occurred in the setting of sinus rhythm.

This hypothesis can be most readily understood if we refer to data on atrial memory[48] and the evolution from atrial memory to atrial tachycardias in an experimental model, as follows.

(1) The normal right and left atria consist of a network, or functional syncytium, of atrial fibers.
(2) The atria incorporate a dominant source of impulse initiation: the sinus node.

(3) Minutes to hours of left atrial pacing induce altered repolarization patterns referred to as atrial memory.[48]
(4) Twenty-four hours of left atrial pacing induce spontaneous arrhythmias, and days to weeks of this same pacing result in the tachycardias persisting long after pacing ceases.[49]
(5) Right atrial pacing induces spontaneous arrhythmias that terminate promptly after cessation of electrical stimulation even after days to weeks of pacing have been imposed.[49]

Considering these elements in light of neural networks, we see emerging a concordant pattern: The rare event, the imposition of left atrial pacing, comes to the fore as a dominant event with regard to the cardiac rhythm expressed. The dominant event, right atrial pacing from a site near the sinus node, ultimately does not perturb the system, resulting in a return to the dominant rhythm.

Moving these same considerations to the clinical arena, we return to the analogy mentioned earlier: the evolution of atrial fibrillation as the result of focal activity in the pulmonary veins.[50] Indeed, the firing of these foci can be likened to the left atrial pacing in the experimental studies.[49] As predicted by the behavior of neural networks, the rare event, the pulmonary venous signal, comes to dominate the system.

Once such initially rare patterns emerge and achieve dominance, the challenge is to discover (or rediscover) the signals required to encourage the return of the formerly dominant and normal pattern. Attempts using various atrial pacing paradigms to prevent recurrences of atrial fibrillation may represent one such approach. Another possible approach draws on what we have learned from the developmental biology of the heart. As stated earlier, the stem cells that are the origin of mature cardiac myocytes are not only capable of exhibiting but do in fact exhibit both normal and abnormal mechanisms for impulse initiation and propagation.[51–53] The signals that suppress potentially pathological events in favor of those that provide organized activation and propagation within the heart are as yet mysteries to us but are no doubt identifiable. As such, each heart is a repository of the mechanisms for normal and abnormal rhythmic function, and we need to learn how to recruit the former.

These thoughts are not meant to denigrate attempts to use pharmacological and other therapies to alter so-called remodeling of myocardium and stress/strain relationships. In the context of the behavior of neural networks, however, such attempts would be considered as acting at the level of modulators of a process rather than at its source. Moreover, answers to the issues raised may also reside in answering such questions as: When is cardiac development complete? What role does aging play in the equation? To what extent does the plasticity seen in neurons characterize the behavior of cardiac myocytes?

These questions are already being explored in research on cardiac structure and function and in those areas of biology that focus on maturation of the conducting system. However, the application of techniques that take advantage of the plasticity of cell systems can be carried still further. For example, neurophysiologists are trying to use their understanding of association by simultaneity to rehabilitate lost function. This approach features simultaneous activation of to-be-joined areas as a means of associating them.[5] It is possible that the lessons derived from these experiments on learning and memory in neuronal networks can also be applied to rehabilitation of rhythm disturbances in heart, not only with respect to atrial arrhythmias but also for ventricular arrhythmias.[54] This attempt to use the biology of one system, the brain, to predict and influence the biology of another, the heart, should at the very least provide new insights and, at best, new therapeutic approaches.

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