On the Role of the cAMP Response Element Binding Protein in Long-Term Cardiac Memory

To the Editor:

Cardiac memory (CM) has been investigated extensively over the last decades.1–3 Whereas early studies focused on electrotonus as a central determinant of cardiac memory,4 more recent work has considered changes in ion channels driven by to-be-determined transcriptional events.4,5 However, any transcriptional mechanisms involved remained largely unidentified. In the September 5 issue of the journal, we reported our first study investigating transcriptional mechanisms of CM.6 Based on previously shown parallels between CM and memory in the CNS,7 which incorporates the cAMP response element binding protein (CREB) as an important transcription factor,8 we investigated the role of CREB in CM. Briefly, using 2 hours of ventricular pacing (VP) to induce short-term CM (STCM), we observed a decrease in nuclear CREB, with phosphorylated CREB levels remaining equal. This decrease was most marked close to the pacing electrode. We also showed reduced binding of nuclear proteins to CRE in dogs in which LTCM was induced by 3 weeks of VP and demonstrated binding of nuclear proteins to a CRE-like element in the Kv4.3 promoter.

An erudite editorial by Folco et al9 in the same issue of the journal notes that several members of the CREB family of transcription factors (including CREM and ATF-1) can compensate for a loss of CREB. They also state that a 50% reduction in CREB is not necessarily adequate to cause loss of function. We fully agree with both points, and accordingly never stated that the 50% CREB reduction observed during 2 hours of VP is responsible for STCM or uniquely responsible for LTCM. However, we do believe and did state (see page 477) that this reduction in CREB might initiate a cascade of events leading to LTCM. It remains to be elucidated whether LTCM would result from events downstream from CREB or from a direct influence of CREB on CM target genes (such as Kv4.3).4 In support of the latter possibility was our observation of nuclear protein binding activity to a CRE-like element in the Kv4.3 promoter region.

Folco and colleagues9 state the Kv4.3 CRE (TGACGTCT) lacks the complete CRE core sequence (CGTCA), and on initial inspection this might seem the case. However, the complementary strand of the Kv4.3 sequence is 5'-AGACGTCA-3', which does contain a CRE core sequence. Whether this element has comparable binding capacities as the consensus CRE is currently under investigation.

Folco and colleagues were puzzled, as were we, that no increase in phosphorylated CREB occurred early in the 2 hours of VP. They offer the explanation that increased phosphorylation might be obscured by a decrease in total nuclear CREB (agreeing with one of the two explanations we provided on page 476). Alternatively, dynamic changes in CREB phosphorylation may have occurred between the time points of the measurements.

In summary, a reduction in CREB activity occurs during pacing to induce STCM. However, this is likely not involved in producing STCM, for which posttranslational rather than transcriptional changes in ion channel regulation are the presumed determinants. We interpret the changes in CREB during this 2-hour pacing period as the beginnings of changes in transcription leading to LTCM. How pacing and/or the alterations in CREB affect the other members of the CREB family are important issues remaining to be investigated.

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