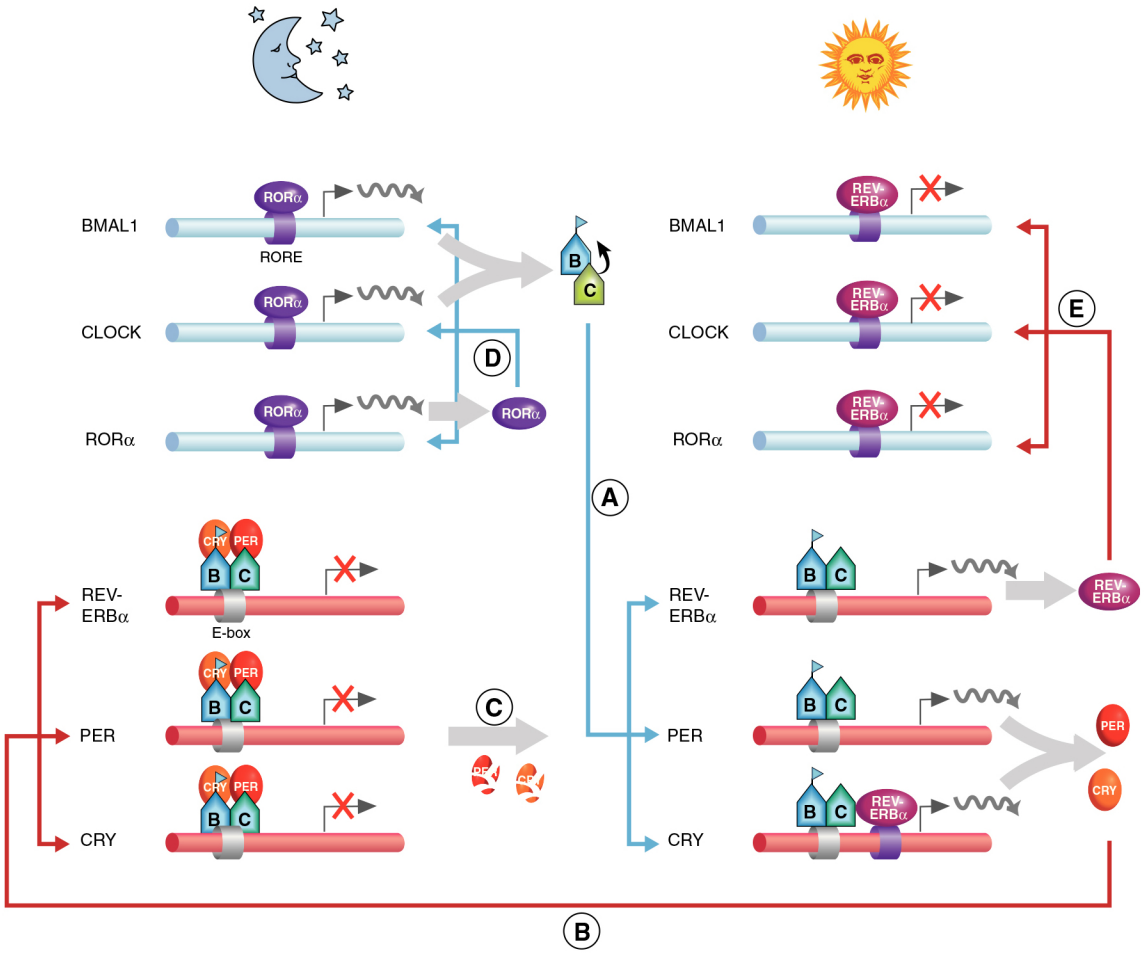

Figure 5. A simplified scheme of the timing of key regulator activity in the molecular circadian clock machinery. (*A*) A maximum accumulation of CLOCK:BMAL1 heterodimers is achieved by daybreak following nighttime transcription and translation. CLOCK:BMAL1 binding to E-box elements of clock-controlled genes (CCGs) leads to chromatin remodeling and activation of genes. (*B*) The daytime expression of the repressors, PER and CRY, partially through the acetylated BMAL1 K537 residue, leads to CCG transcriptional repression at night. (*C*) The nighttime degradation of PER/CRY repression gradually leads to the derepression of CCGs by daybreak. (*D*) At nighttime, the predominance of RORα binding to the RORE (retinoic acid–related orphan receptor response element) lends to transcription of BMAL1, CLOCK, and RORα. (*E*) The predominance of REV-ERBα, as a result of the gene's daytime transcription, has an inhibitory action on BMAL1, CLOCK, and RORα.