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Structure of a General Anesthetic Binding Site on PKC. S.Shanmugasundararaj, J.Das and K.W. Miller, Dep.t of Anesthesia, MGH, Boston, MA, 02114.

Anesthetics are relatively nonspecific drugs that interact with many transmembrane ion channels and soluble proteins, often causing unwanted side effects. Gaining a detailed understanding of the structural motifs governing anesthetic-protein interactions is a critical step in elucidating the molecular mechanisms underlying general anesthesia. General anesthetics modulate phorbol ester binding and are therefore hypothesized to interact with the cysteine-rich diacylglycerol/phorbol ester-binding domain, C1 of protein kinase C, a tandem repeat of C1A and C1B subdomains. We have solved the crystal structure of the high affinity phorbol-binding subdomain, C1B of mouse PKC in the absence and presence of anesthetics and studied its interaction with general anesthetic alcohols. The cell parameters are $a=43.715$; $b=32.597$; $c=49.719\text{\AA}$ and $\beta=94.2$;There is an anesthetic-binding pocket that is bounded by (Tyr-236, Asn-237, Tyr-238, Met-239 and Ser-240). This pocket is separated from the phorbol-binding pocket by a single strand of residues that include Met-239 and Ser-240. Mutations in this pocket designed to ablate or enhance general anesthetic binding would provide a powerful method for testing the hypothesis proposed above in cells and animals.

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