S 10-3

ROLE OF cAMP SIGNALING IN INSULIN GRANULE EXOCYTOSIS

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Insulin, a central hormone of glucose homeostasis, is secreted from pancreatic β-cells. Insulin secretion is regulated by various intracellular signals, including calcium, ATP, cAMP, and GTP-binding proteins. Among them, cAMP is known to play an important role in the potentiation of insulin secretion. We recently have found that cAMP potentiates insulin granule exocytosis by PKA-independent as well as by PKA-dependent mechanisms. The PKA-independent mechanism is mediated by the cAMP-binding protein cAMP-GEFII (also called Epac2). cAMP-GEFII-mediated insulin granule exocytosis requires the interaction of cAMP-GEFII with Piccolo and Rim2. cAMP signals are now known to be localized in distinct microdomains or functional compartments (cAMP compartmentation). G-protein coupled receptors, GTP-binding proteins, adenylyl cyclase isoforms, PDE isoforms, phosphoprotein phosphatases, AKAP isoforms, and PKA substrates all contribute to cAMP compartmentation associated with PKA signaling, as proposed for cardiomyocytes. We hypothesize that cAMP-GEFII resides in a cAMP compartment distinct from that containing PKA. Because cAMP-GEFII has a lower affinity for cAMP than for PKA, a much higher concentration of cAMP might accumulate in the cAMP compartment in which cAMP-GEFII-mediated signaling occurs. We are currently investigating the temporal and spatial regulation of insulin granule exocytosis, using yellow fluorescence protein (Venus) fused with insulin (insulin-Venus) in combination with total internal reflection fluorescence (TIRF) microscopy. In this symposium, I will discuss the role of cAMP signaling in the temporal and spatial regulation of insulin granule exocytosis.

S 11-1

CLIMBING FIBER AXONS IN THE ADULT CEREBELLAR CORTEX DISPLAY BRANCH TYPE-SPECIFIC MOTILITY

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Recently, imaging studies have revealed that motile axons are present in the neocortex of adult mice and monkeys. However, the principles governing axonal motility in the adult brain remain largely unexplored. For example, does axonal motility depend only upon the presynaptic cell of origin or it is also influenced by the axon's postsynaptic targets? To address this question, we performed two-photon in vivo imaging of cerebellar climbing fibers (CFs; the terminal arbor of olivocerebellar axons) in adult mice. CF ascending branches innervate Purkinje cells while thin transverse branches have been suggested to innervate interneurons. Time-lapse imaging over several hours revealed that ascending branches were almost completely stable. However, transverse branches were highly dynamic, exhibiting rapid elongation and retraction (~25% of total branches) and varicosity turnover (~30% of total varicosities). Thus, different branches of the same axon, which innervate different targets, display branch type-specific motility in the adult cerebellum.