THE STUDY OF BIOLOGICAL ACTIVITY OF SYNTHETIC INHIBITORS OF JNK KINASE

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c-Jun N-terminal protein kinases (JNK), also known as stress-activated protein kinases, were originally identified by their ability to phosphorylate the N-terminal of the transcription factor c-Jun and by their activation in response to a variety of stresses (such as heat, pH variation, radiation, redox, osmolality, and chemical stimulation such as growth factors, cytokines, hormones, alterations in nutrient conditions, as well as other environment stresses).Activation of JNK also underlies the development of pathological conditions such as NAFAD,obesity, atherosclerosis. JNK kinases are an important target in the treatment of various dyslipidemic conditions. They belong to the mitogen-activated protein kinase family, and are responsive to stress stimuli, such as cytokines, ultraviolet irradiation, heat shock, and osmotic shock. They also play a role in T cell differentiation and the cellular apoptosis pathway. Activation occurs through a dual phosphorylation of threonine (Thr) and tyrosine (Tyr) residues within a Thr-Pro-Tyr motif located in kinase sub domain VIII. Activation is carried out by two MAP kinases, MKK4 and MKK7 and JNK can be inactivated by Ser/Thr and Tyr protein phosphates. It has been suggested that this signaling pathway contributes to inflammatory responses in mammals and insects. The c-Jun N-terminal kinases consist of ten isoforms derived from three genes: JNK1 (four isoforms), JNK2 (four isoforms) and JNK3 (two isoforms). Each gene is expressed as either 46 kDa or 55 kDa protein kinases, depending upon how the 3' coding region of the corresponding mRNA is processed. There have been no functional differences documented between the 46 kDa and the 55 kDa isoform, however, a second form of alternative splicing occurs within transcripts of JNK1 and JNK2, yielding JNK1-α, JNK2-α and JNK1-β and JNK2-β. Differences in interactions with protein substrates arise because of the mutually exclusive utilization of two axons within the kinase domain.c-Jun N-terminal kinase isoforms have the following tissue distribution:JNK1 and JNK2 are found in all cells and tissues.JNK3 is found mainly in the brain, but is also found in the heart and the testes. Function Inflammatory signals, changes in levels of reactive oxygen species, ultraviolet radiation, protein synthesis inhibitors, and a variety of stress stimuli can activate JNK. One way this activation may occur is through disruption of the conformation of sensitive protein phosphates enzymes; specific phosphates normally inhibit the activity of JNK itself and the activity of proteins linked to JNK activation.JNKs can associate with scaffold proteins JNK interacting proteins as well as their upstream kinases JNKK1 and JNKK2 following their activation.JNK, by phosphorylation, modifies the activity of numerous proteins that reside at the mitochondria or act in the nucleus. Downstream molecules that are activated by JNK include c-Jun, ATF2, ELK1, SMAD4, p53 and HSF1. The downstream molecules that are inhibited by JNK activation include NFAT4, NFATC1 and STAT3. By activating and inhibiting other small molecules in this way,JNK activity regulates several important cellular functions including cell growth, differentiation, survival and apoptosis.JNK1 is involved in apoptosis, neurodegeneration, cell differentiation and proliferation, inflammatory conditions and cytokine production mediated by AP-1 such as RANTES, IL-8