Reduced threshold for cortical spreading depression in mice expressing human CK1δ T44A

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Cortical spreading depression

Leao A.A.P. 1944
Leao A.A.P. 1944a

van den Maagdenberg AM et al., Neuron 2004
CK1δ mutation causes familial advanced sleep phase syndrome (FASPS)

A to G mutation in DNA sequence, threonine to alanine substitution at AA 44
Decreased kinase activity in vitro; decreased $V_{max}$ and $K_m$
Circadian phenotype in fly and mouse
-longer $\tau$ in fly, shorter in mouse

6 affected family members
-advanced sleep phase
-shorter period ($\tau$)

Xu Y. et al., Nature 2005

Casein Kinase 1δ and Migraine

A novel familial syndrome of migraine with aura, flushing spells, myalgias, asthuma, and the advanced sleep phase syndrome. RE Skupiro, W Waheed, K Nagle. Department of Neurology, College of Medicine, University of Vermont, Burlington, Vt, 05405, USA

Casein Kinase 1δ and Migraine

-patients’ chief complaint was migraine with aura!
Optical intrinsic signal imaging (OIS)  
Cortical spreading depression protocol

Optical intrinsic signal imaging of cortical spreading depression in mouse  
(2 Hz acquisition, 60 Hz playback)
Hypothesis:

- Decreased threshold for CSD in CK1δT44A mutants
Lower threshold for CSD induction in CK1δ T44A mutants

![Graph showing CSD threshold (PSI) for Wild Type and CK1δ T44A with different KCl concentrations and sample sizes.]

Same rate of CSD induction per experiment

![Graph showing # CSD per Experiment for Wild Type and CK1δ T44A with sample sizes and p-value.]

Wild Type: n = 8, p = 0.36

CK1δ T44A: n = 11, p = 0.004
Greater efficiency of CSD induction in CK1δ T44A mutants

![Graph showing CSD induction efficiency](image)

Different arteriolar response to CSD in CK1δ T44A mutants

![Graph showing arteriolar response](image)
Questions

• Is CK1δ responsible for increased sensitivity to CSD?
  – Modulation of glutamate neurotransmission?
    • activation of CK1 decreases NMDA receptor activity via PP1,2a (Chergui K 2005)
  – Modulation of connexin43?
    • CK1 inhibition results in increased membrane localization of Cx43 hemichannels. (Cooper CD 2002)

• Why vasodilatation?
  – Disorder of smooth muscle cell function?
    • Affected family members have bronchospasm, flushing
    • CK1 phosphorylates smooth muscle myosin light chain (Singh TJ 1983)
    • CK1 phosphorylates C3a (anaphylatoxin) (Kawakami F 2004)
    • CK1 upregulated in intimal hyperplasia (Itoh M 1998)

Conclusions

• Lower CSD threshold, greater efficiency of CSD induction, increased arteriolar dilatation during CSD in CK1δ tranenics
• Suggests novel actor in pathogenesis of migraine, possible animal model of non-hemiplegic migraine
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