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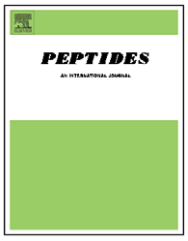

FMRFamide-gated sodium channel and ASIC channels: A new class of ionotropic receptors for FMRFamide and related peptides

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FaNaC, FMRFamide-activated Na^+ channel
HaFaNaC, *Helix aspersa* FaNaC
HtFaNaC, *Helisoma trivolvis* FaNaC
LsFaNaC, *Lymnaea stagnalis* FaNaC
AkFaNaC, *Aplysia kurodai* FaNaC
ASIC, acid-sensing ion channel
ENaC/DEG, epithelial amiloride-sensitive Na^+ channels and degenerins
NPFF, neuropeptide FF (FLFQPQRFamide)
NPSF, neuropeptide SF (SLAAPQRFamide)
RFRP-1, VPHSAANLPLRFamide
RFRP-2, SHFPSLPQRFamide
PF4, KPNFIRFamide
GDN, giant dopamine neuron
LSN, large serotonin neuron

ABSTRACT

FMRFamide and related peptides typically exert their action through G-protein coupled receptors. However, two ionotropic receptors for these peptides have recently been identified. They are both members of the epithelial amiloride-sensitive Na^+ channel and degenerin (ENaC/DEG) family of ion channels. The invertebrate FMRFamide-gated Na^+ channel (FaNaC) is a neuronal Na^+-selective channel which is directly gated by micromolar concentrations of FMRFamide and related tetrapeptides. Its response is fast and partially desensitizing, and FaNaC has been proposed to participate in peptidergic neurotransmission. On the other hand, mammalian acid-sensing ion channels (ASICs) are not gated but are directly modulated by FMRFamide and related mammalian peptides like NPFF and NPSF. ASICs are activated by external protons and are therefore extracellular pH sensors. They are expressed both in the central and peripheral nervous system and appear to be involved in many physiological and pathophysiological processes such as hippocampal long-term potentiation and defects in learning and memory, acquired fear-related behavior, retinal function, brain ischemia, pain sensation in ischemia and inflammation, taste perception, hearing functions, and mechanoperception. The potentiation of ASIC activity by endogenous RFamide neuropeptides probably participates in the response to noxious acidosis in sensory and central neurons. Available data also raises the possibility of the existence of still unknown FMRFamide related endogenous peptides acting as direct agonists for ASICs.

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RpeD1, right pedal dorsal 1
DRG, dorsal root ganglion
EIPA, ethylisopropylamiloride
PcTx1, Psalmotoxin 1
PDZ, post-synaptic density-95, Drosophila discs-large, zonula occludens-1
PICK1, protein interacting with C-kinase-1
CIPP, channel-interacting PDZ domain protein
NHERF-1, Na^+/H^+ exchanger regulatory factor-1
PSD-95, post-synaptic density-95 protein
TM1, first transmembrane domain

Introduction

FMRFamide and structurally related peptides are abundant in invertebrate nervous systems where they have been proposed to function as neurotransmitters and neuromodulators [47,144]. FMRFamide itself has not been isolated in mammals but several FMRFamide-related peptides exist in the mammalian nervous system. FMRFamide has been recently shown to directly modulate the function of two ion channels: the invertebrate FMRFamide-gated Na^+ channel FaNaC and the mammalian acid-sensing ion channel ASIC. This review proposes to discuss the properties of these two important channels in relation with FMRFamide and related peptides.

1. FMRFamide-activated Na^+ channel (FaNaC)

Most of the neuronal actions of FMRFamide are mediated through G-protein coupled receptors. However, some identified neurons of the snails *Helix aspersa* [45,48,82] and *Helisoma trivolvis* [98], and of *Aplysia californica* [22,156] and *Lymnaea stagnalis* [140,159] display a fast depolarizing response to FMRFamide application through activation of a sodium conductance. Outside-out membrane patch recordings from the *Helix* C2 neuron provide evidence that FMRFamide directly gates Na^+ channels with no involvement of G-proteins [82]. A PCR-based homology approach led to the molecular cloning of the corresponding channel from *Helix* neurons [119], which has been named FaNaC (FMRFamide-activated Na^+ channel, designated here as HaFaNaC). More recently, FaNaC has been cloned from three other species: HtFaNaC from the pond snail *Helisoma trivolvis* [98], LsFaNaC from *Lymnaea stagnalis* [140] and AkFaNaC from *Aplysia kurodai* [74]. FaNaC represents the first, and to date unique, member of a new class of ionotropic receptors directly gated by peptides.

1.1. *Properties of FaNaC*

HaFaNaC, HtFaNaC and AkFaNaC are able to generate a large FMRFamide-induced inward current when expressed in *Xenopus* oocytes and mammalian cells (Fig. 1) [43,74,98,119,194]. Although LsFaNaC has not been expressed in vitro, one would expect a similar behavior. External application of FMRFamide induces a fast and partially desensitizing current ($EC_{50} \sim 2$, 4 and 70 μM for HaFaNaC, AkFaNaC and HtFaNaC, respectively). Single channel analyses reveal a major open time constant in the millisecond range (4 and 0.7 ms for HaFaNaC and HtFaNaC, respectively). FaNaC is highly selective for Na^+ versus K^+ and Ca^{2+} ($P_{Na^+}/P_{K^+} > 10$), and has

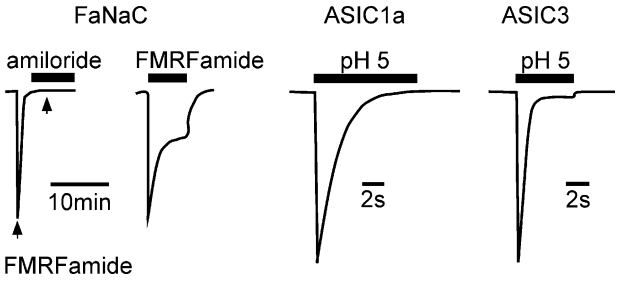

Fig. 1 – Typical current traces for FaNaC and ASIC channels. Schematic representation of typical inward current traces recorded from recombinant channels expressed in *Xenopus* oocytes (FaNaC) or mammalian cell lines (ASICs). FaNaC currents are elicited by brief (arrows on the first trace) or continuous (horizontal bar above the second trace) application of FMRFamide. ASIC1a and ASIC3 homomeric channel activity is induced by low pH application from neutral pH, indicated by the bars above each current trace. Amiloride inhibition of the FaNaC current is also shown (horizontal bar above the first trace). Note the fast and partially desensitizing response of FaNaC and the difference between ASIC1a and ASIC3 currents. ASIC3-containing channels have an additional slowly activating component that does not inactivate and is smaller than the transient component [186]. Combination of ASIC3 with the modulatory subunit ASIC2b modifies the pH dependence and the ion selectivity of the sustained current [120].