

PLENARY PRESENTATIONS

NATURAL PEPTIDE MODULATORS OF TRPA1 AND TRPV1 CHANNELS INCREASES LONG-TERM POTENTIATION IN THE HIPPOCAMPUS AND REDUCES ANXIETY AND FEAR IN MICE

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TRPA1 and TRPV1 channels are well-characterized in peripheral nociceptive neurons, yet their functional roles in the brain remain comparatively obscure. While these channels have been implicated in modulating neurotransmitter release at certain central synapses, their involvement in the central response to acute stress is not well defined. Here, we investigated this role by examining the effects of two TRPV1 antagonists (AMG517 and APHC3) and a positive TRPA1 modulator (peptide Ms9a-1) on hippocampal synaptic plasticity. We measured paired-pulse ratio (PPR) and field excitatory postsynaptic potentials (fEPSPs) following long-term potentiation (LTP) induction in the hippocampal CA3-CA1 pathway. Additionally, we evaluated anxiety-like behaviors in the elevated plus maze and light/dark box tests, comparing the peptide treatments to the reference anxiolytic and neuroprotective drug, Fabomotizole.

To differentiate between central and peripheral mechanisms, Ms9a-1 and APHC3 were administered both intramuscularly (i.m.), to restrict action to the peripheral nervous system (PNS), and intranasally (i.n.), to facilitate brain delivery. In electrophysiological recordings, APHC3 significantly enhanced both LTP and PPR, whereas Ms9a-1 and AMG517 enhanced PPR alone. Behaviorally, all three compounds improved stress-test performance to a degree comparable to Fab, confirming a significant contribution of both TRPV1 and TRPA1 channels to the stress response.

Notably, i.m. APHC3 produced a more pronounced and consistent anxiolytic effect than its intranasal administration, underscoring the critical role of peripheral nociceptor signaling in mediating the anxiolytic properties of TRPV1 modulation. In contrast, the effects of Ms9a-1 were weaker, suggesting a comparatively minor involvement of TRPA1 in acute stress. We propose that peripheral inhibition of TRPV1 and TRPA1 by AMG517, APHC3, or Ms9a-1 alters primary afferent signaling, thereby modulating the behavioral response to stress. The robust efficacy of i.m. APHC3 and Ms9a-1 is likely mediated through their action on afferent neurons. Intranasal delivery, however, showed only moderate efficacy and appeared effective within a narrow dose range. We interpret this reduced efficacy not as a failure of CNS bioavailability, but rather as a distinct pharmacodynamic profile, where the intranasal route elicits a biphasic, dose-dependent response with an optimal anxiolytic window.

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