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PAMs: A Growing Field in Pharmacological Drug Development

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Positive Allosteric Modulators (PAMs) are a growing field in pharmacology. PAM-5 and genistein cause acetylcholine (ACh) to elicit larger currents on nicotinic acetylcholine receptors (nAChRs) without activating the channel themselves. In effect, PAMs increase the amplitude of currents at a synapse without altering the normal firing rate of the neurons.

**METHODS**

Plasmids containing human α7 and β2 nAChR genes were linearized by restriction digest with SacI (New England BioLabs). The mRNA was then transcribed, capped on the 5’ end, a poly(A) tail was added, and LiCL purification was performed using the mMessage mMachine® T7 Ultra Kit (Ambion, Carlsbad CA) according to the protocol provided. RNA was re-suspended in TE Buffer (Bioexpress, Layton UT) and stored at -20°C.

Each oocyte was injected with 50 nL of mRNA for a total of 75 ng of mRNA per oocyte. Homomeric α7 expression requires α7 mRNA injection only while the α7β2 subunit requires injection of a 1:1 mix of α7 and β2 mRNA. The oocytes were stored a solution of OR2-2Ca²⁺ at 14-17°C until recordings were obtained 7-9 days later.

Recordings were obtained through two-electrode voltage clamp (Figure 1). Traces were recorded using Clampex 9.2 software (Axon Instruments, Sunnyvale CA) and analyzed on ClampFit 9.2 (Axon Instruments, Sunnyvale CA). Solutions containing acetylcholine and the various PAMs were perfused over the oocyte at room temperature.

**CONCLUSIONS**

- PAM-5 and genistein act on α7 nAChRs and likely on α7β2 nAChRs as well.
- PAMs may help strengthen the communication at weakening synapses due to increased communication.
- PAMs could serve as treatments for cognitive disorders such as Alzheimer’s disease where a decrease in cholinergic signaling occurs.
- PAMs could serve as a way to differentiate nAChR subtypes for in vivo electrophysiology recordings.