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**170.9**

**[3H]A-778317: a novel high-affinity radioligand for the TRPV1 receptor**

Bruce Robert Bianchi, Rachid El Kouhen, Chih-Hung Lee, Shirish N. Raja, Srirajan Vaidyanathan, Bruce Surber, Connie R. Faltynek, Pamela S. Puttfarcken, Robert B. Moreland. Neuroscience Research, Abbott, 100 Abbott Park Rd, Abbott Park, IL, 60064

A-778317 is a potent and competitive antagonist of capsaicin at the TRPV1 receptor. In the present studies, we investigated the binding properties of [$^3$H]A-778317 in membrane preparations of human TRPV1-expressing CHO cells and different rat brain regions. [$^3$H]A-778317 labeled a single class of binding sites in human TRPV1-expressing CHO cell membranes with high affinity ($K_D$ = 3.39 nM and $B_{max}$ = 4.02 pmol/mg protein). A minor amount of specific [$^3$H]A-778317 binding was also detected in untransfected CHO cell membranes comprising about 15% of the total specific bound counts in human TRPV1-expressing CHO cell membranes, and likely represents binding to a native nonfunctional TRPV1 splice variant. Specific binding of [$^3$H]A-778317 in human TRPV1-expressing CHO cell membranes was reversible, and inhibited completely by several TRPV1 agonists and antagonists. The potencies of the different TRPV1 ligands to inhibit [$^3$H]A-778317 binding correlated well with functional potencies in a cell-based $Ca^{2+}$influx assay (goodness of fit $r^2$ = 0.789), with the exception of capsaicin. The TRPV1 agonist capsaicin was found to be a weak inhibitor of binding ($K_i$ = 25.6 μM), yet potently stimulated $Ca^{2+}$ influx in hTRPV1-expressing CHO cells ($EC_{50}$ = 30.9 nM). Specific binding of [$^3$H]A-778317 was also demonstrable in membrane preparations of different rat brain regions, and similarly, it appeared to label a single class of high-affinity binding sites ($K_D$ = 8-13 nM). Rank order of $B_{max}$ was hippocampus > cerebellum ≥ cerebral cortex > hypothalamus > spinal cord. Supported by Abbott.

**170.10**

**Attenuation of DOI-induced head twitches in mGluR2 KO mice**

Mark Joseph Benvenga[1], Stephen F. Chaney[1], Melvin Baez[1], Thomas C. Britton[2], William J. Hornback[2], James A. Monn[2], Gerard J. Marek[1]. [1]Neuroscience Discovery Research, [2]Chemistry Discovery Research, Eli Lilly & Company, Mail Code 0510, Lilly Corp Ctr, Indianapolis, IN, 46285

There is substantial pharmacological evidence that glutamate can modulate the effects of 5-hydroxytryptamine$_{2A}$ (5-$HT_{2A}$) receptor activation through stimulation of metabotropic glutamate2/3 receptors (mGluR2/3) in the cerebral cortex. In this work, we show that deletion of mGluR2 profoundly attenuates the head twitch behavior elicited by 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) administration in mice.

MGlu2 KO and age-matched ICR (CD-1) WT mice (N=8/dose) were administered DOI and observed for head twitch activity over 30 minutes. Additional CD-1 mice were administered the mGluR2/3 agonist LY379268 or the mGluR2 potentiator LY566332 followed by DOI, and observed for head twitches for 30 minutes. The results indicated that both LY379268 and LY566332 were able to reduce head twitches in a dose-dependent manner. More importantly, DOI (3mg/kg) failed to elicit head twitches in the mGlu2 KO mice where even a 30 mg/kg dose produced a head shake frequency only ~ 25% of that seen in WT mice.

These results indicate that the mGluR2 receptor is intimately involved in modulating head twitches elicited by the 5-$HT_{2A}$ agonist DOI. This behavior, coupled with past electrophysiological, behavioral and biochemical results, suggests that mGluR2 functions as an autoreceptor in thalamocortical pathways impinging upon the principal output cells, layer V pyramidal cells, of the mPFC.

**170.11**

**α adrenergic activation of GABAergic interneurons in region CA1 of the rat hippocampus**

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Heightened cellular activity in the hippocampus is implicated in a majority of temporal lobe epilepsies. In vitro, application of the catecholamine norepinephrine (NE) to hippocampal slices reduces experimentally-induced seizure activity. We hypothesize NE exerts this antiepileptic effect in part through adrenergic activation of inhibitory GABAergic interneurons. Using cell-attached recordings and single cell RT-PCR, we have identified a subset of GABAergic interneurons in hippocampal region CA1 that express α1 adrenergic receptors (ARs). Application of the selective αAR agonist 6-fluoronorepinephrine (6FNE) elicited an increase in action potential frequency in these cells (EC50 11μM). Pre-treatment with 100nM of the α1 selective AR antagonist prazosin produced a significant rightward shift in the concentration response curve for 6FNE (EC50 221μM), an effect not seen when slices were pre-treated with 100nM of the α2 selective AR antagonist rauwolscine (EC50 6.3μM), suggesting 6FNE is acting predominately through an α1 AR in these cells. RT-PCR analysis of cytoplasm extracted from recorded cells revealed mRNA expression of the α1A AR, the α1B AR, or co-expression of both receptors. Neuropeptide expression was also examined in the cytoplasmic samples and interestingly all 6FNE-responsive interneurons were positive for somatostatin. Together, these results begin to define a cellular subset within the hippocampus that likely contributes to NE's antiepileptic effect. Support: American Epilepsy Society, NSF CAREER 0347259, ND EPSCoR NSF EPS-0447679 and NIH 5P20RR017699

## GPCR SIGNALING I (171.1-171.16)

**171.1**

**Transmembrane five effects on functional selectivity at the dopamine D2L receptor**

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Mechanisms of functional selectivity (ligand-induced differential signaling) at the dopamine D2 receptor were studied by addressing how binding interactions at specific amino acids affect ligand function. Molecular modeling was used to dock the structurally similar compounds dinapsoline (DNS) and dinoxyline (DNX) into the active site of the hD2L receptor, after which point mutants of the receptor were made to test each hypothesis. Binding studies conducted with DNS support H bonding of the p-OH with both serine 5.46(197) and threonine 3.37(119) whereas the m-OH interacts with serine 5.42(193). Conversely, data with DNX supports H-bonding of the p-OH with only T3.37 whereas the m-OH interacts with both serine 5.42 and 5.46. Additionally, an ether internal to DNX also forms H-bonds with serine 5.42. Subsequent functional analyses of site-directed mutant receptors support the hypothesis that specific ligand-residue interactions can affect the observed functional differences in cAMP inhibition, MAPK phosphorylation, and AA-release. Developing a structure-based understanding of functional selectivity is heuristically useful for understanding the mechanisms of GPCR activation, and also may suggest the design of novel small molecules with unique mixtures of functional properties.

**171.2**

**THE ROLE OF THREONINE3.37 [T3.37] IN D1-LIKE DOPAMINE RECEPTOR ACTIVATION**

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The molecular mechanisms by which agonists bind and activate GPCRs in general, and the $D_1$ and $D_5$ dopamine receptors in particular, is largely unknown. Molecular modeling of the $D_1$-like receptors lead to the hypothesis that in the $D_1$ receptor, T3.37 may be positioned to interact with the para-OH of $D_1$ receptor ligands. To investigate this hypothesis, a non-conservative mutation (to alanine) of T3.37 was made to examine the role this residue plays in ligand binding and receptor activation. After site-directed mutagenesis, rationally selected, structurally dissimilar probe ligands [e.g., SCH23390, dopamine, dihydrexidine