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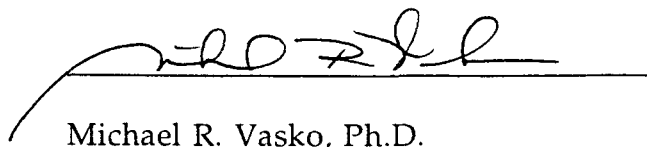
PROSTAGLANDIN E₂ AND INCREASES IN INTRACELLULAR
CYCLIC AMP ENHANCE THE BRADYKININ-STIMULATED
RELEASE OF SUBSTANCE P AND CGRP FROM RAT SENSORY
NEURONS IN CULTURE

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Submitted to the faculty of the University Graduate School
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for the degree
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in the Department of Pharmacology and Toxicology,
Indiana University

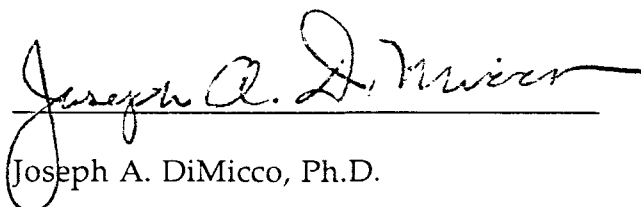
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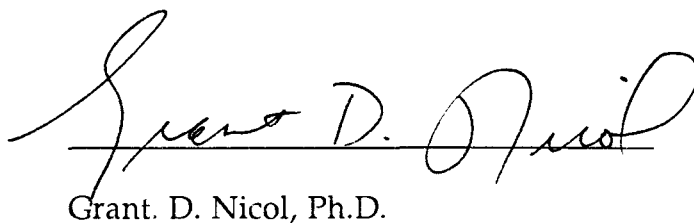


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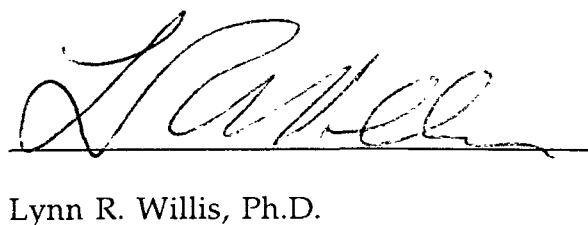
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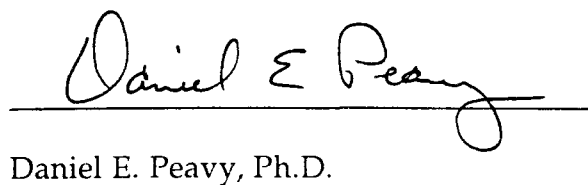
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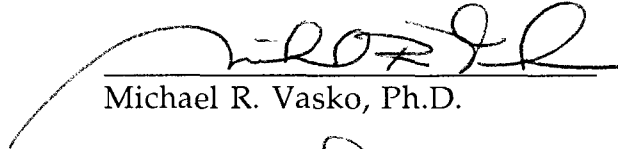
ABSTRACT

Prostaglandin E₂ (PGE₂) increases the number of action potentials produced in sensory neurons by application of bradykinin. Furthermore, PGE₂ lowers the pain threshold (i.e. produces hyperalgesia) and enhances the pain-producing effects of bradykinin. One possible mechanism to explain this enhanced nociception is that PGE₂ increases the bradykinin-stimulated release of neurotransmitters from nociceptive sensory neurons. To test this hypothesis, I studied the effects of PGE₂ on resting and bradykinin-evoked release of substance P (SP) and calcitonin gene-related peptide (CGRP) from rat sensory neurons grown in culture.

Addition of 5 and 10 μ M PGE₂ to the cells significantly increased SP release; however, lower concentrations of PGE₂ (10 nM to 1 μ M) significantly enhanced the bradykinin-stimulated release of both SP and CGRP from cultured sensory neurons. During experiments performed to probe the second messenger system involved in this sensitization, it was shown that PGE₂ increases intracellular cyclic AMP in these cultured sensory neurons. Increases in intracellular cyclic AMP concentration mimicked PGE₂-mediated enhancement of bradykinin-stimulated release. THFA (9-(tetrahydro-2-furyl)adenine) fully inhibited the PGE₂-stimulated synthesis of cyclic AMP, and abolished PGE₂-mediated enhancement of bradykinin-stimulated neurotransmitter release. THFA also inhibited bradykinin-evoked release of SP and CGRP from these neurons.

These results demonstrate that PGE₂ enhances release of neurotransmitters from rat sensory neurons. Furthermore, a likely mechanism by which PGE₂ mediates this effect may involve increases in intracellular cyclic AMP. It is

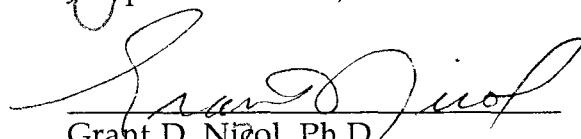
probable that this enhancement of neurotransmitter release contributes to PGE₂-induced hyperalgesia.



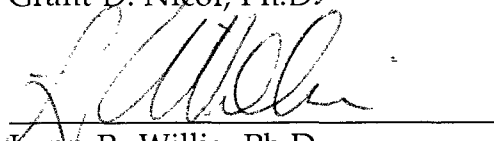
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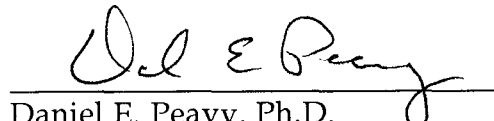
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