ABSTRACT

Involvement of Nitric Oxide (NO) and Guanosine 3', 5' Cyclic Monophosphate (cyclic GMP) in the Modulation of Uterine Contractions.

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Although nitric oxide (NO) donors are considered by some to be a potentially beneficial group of drugs for arresting premature labour and maintaining uterine quiescence during pregnancy, controversy surrounds the level of NO involvement and its mechanism of action in the modulation of uterine contractions.

A proposed mechanism of inhibition of myometrial contractions by NO is the activation of guanylate cyclase, leading to increased intracellular levels of guanosine 3', 5' cyclic monophosphate (cyclic GMP) and relaxation (Yallampalli et al., 1993 & 1994; Izumi et al., 1993). However, evidence has also been presented against the operation of this system in the uterus (Kuenzli et al., 1996 & 1998; Bradley et al., 1998).

The present study seeks to determine whether NO may be involved in the modulation of uterine contractions in rats and mice, and whether this effect is dependent on guanylate cyclase activation leading to elevated intracellular levels of cyclic GMP.

The hypothetical basis of this study is: if NO activates guanylate cyclase to produce uterine relaxation via increased synthesis of cyclic GMP, then inhibition of guanylate cyclase should inhibit the ability of NO to increase intracellular levels of cyclic GMP, and should also inhibit the ability to relax uterine muscle.

In vitro studies were performed on uterine longitudinal muscle strips obtained from pregnant and non-pregnant rats, and pregnant mice. Uterine strips were exposed to several agents which alter tissue levels of NO and cyclic GMP, and the effects of these agents on spontaneous and acetylcholine- evoked contractions were determined by monitoring isometric tension developed in the muscle strips. Tissue levels of cyclic GMP were measured by ELISA technique.

The findings presented indicate that although NO and cyclic GMP attenuate spontaneous and acetylcholine- evoked uterine contractions, blockade of guanylate cyclase inhibits the synthesis of cyclic GMP without inhibiting the ability of NO to produce relaxation. In fact, the results of this study suggest

that NO attenuates uterine contractions in rats and mice by a mechanism that is not dependent on guanylate cyclase activation and increases in intracellular levels of cyclic GMP.

A schematic representation of the central hypothesis and results of the study is as follows: