

# An Overview on the Respiratory Stimulant Effects of Caffeine and Progesterone on Response to Hypoxia and Apnea Frequency in Developing Rats

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## Abstract

The respiratory stimulant caffeine is the most frequently used xanthine (theophylline or aminophylline) for the treatment of apnea in premature infants. It decreases but does not eliminate apnea. In most cases such decreases is insufficient to prevent the use of artificial ventilation.

**Progesterone is a respiratory stimulant in adult mammals including human, and it decreases sleep apnea in menopausal women.** Whether progesterone as an adjunct to caffeine therapy could be effective in further reducing the frequency of apnea in premature infants is not known because its respiratory effect in newborns has not been well studied. Using rat pups at different postnatal ages, we first determined whether the respiratory stimulant effects of acute caffeine (10 mg/kg, i.p.) or progesterone (4 mg/kg i.p.) are age dependent. These studies showed that caffeine enhances the ventilatory response to hypoxia in 1 and 4 days-old rats while it decreases apnea frequency in 12-days-old. In contrast, progesterone enhances the ventilatory response to hypoxia in less than 7-days-old but decreases apnea in 1-day-old rats. Preliminary experiments show that administration of progesterone (4 mg/kg i.p.) to newborn rats that are chronically treated with caffeine (mimicking its clinical uses - 7.5 mg/kg once/day by gavage) enhances the respiratory stimulant effects of caffeine. Surprisingly, acute injection of progesterone enhances apnea frequency and reduces hypoxic ventilatory response in 12-day-old rats.

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