CLINICAL STUDIES WITH MARIHUANA AND DEXTROAMPHETAMINE COMBINATION

EVANS, Michael Allan, Ph.D.
Indiana University, 1974

Studies in mice indicated that delta-9-tetrahydrocannabinol (THC) significantly enhanced methamphetamine induced locomotor activity. The effect was dose related with maximal interaction for THC at an i.p. dose of 15 mg/kg. To investigate the possibility of marihuana-amphetamine interaction in man, experimental protocol and psychometric test equipment were established to quantitatively measure drug induced behavioral changes. The test equipment included: the Wobble Board to monitor standing steadiness; the Pursuit Meter, to assess attentive motor performance; the Delayed Auditory Feedback, to measure changes in mental performance; the Suitcase Instrument, to evaluate manual dexterity, reaction time and fine muscle control; the Modified Cornell Medical Index, to determine the subjective intensity of drug action and the Addiction Research Inventory Scale to evaluate the subjective nature of drug action. Clinical dose response studies with ethanol and secobarbital demonstrated that under the established protocol, quantitative changes in psychomotor performance could be determined by the test equipment. Ethanol in oral doses of 25, 40, 55 and 70 ml/70 kg produced a significant blood alcohol concentration related impairment in performance for 23 of 26 administered tests. Secobarbital at oral doses of 50, 100 and 150 mg/70 kg also produced a dose related increase in test scores; however significant impairment was observed only at the high dose of 150 mg/70 kg. Marihuana cigarettes designed to deliver doses of 3, 6 or 9 ug/kg THC produced only a significant decrease in stability and attentive motor performance. Dextroamphetamine in oral doses of 5, 10 and 15 mg/kg on the other hand produced no consistent change in test scores and isolated tests involving simple reaction time suggested a slight improvement in performance. A cardiovascular study of marihuana at 50 ug/kg THC and d-amphetamine at 10 mg/70 kg demonstrated that the combination produced no effect above simple addition on heart rate (HR), blood pressure (BP), ECG changes and symptom scores. THC produced an increase in HR of 35 beats/min. and d-amphetamine produced a systolic BP of 130 mm Hg. Psychometric evaluation of marihuana 25 ug/kg THC and 10 mg/70 kg amphetamine combination, indicated that the stimulant failed to change the marihuana induced impairment of performance. Psychological changes as monitored by symptom scores demonstrated additivity in drug effects. These studies suggest that higher doses of marihuana amphetamine combination may produce harmful psychological and cardiovascular effects but not above that of simple addition. The use of stimulants failed to alleviate the performance decrements produced by marihuana smoking, suggesting that THC impairment is not related to sedation or fatigue.

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INTERACTIONS AMONG NARCOTICS, NEUROTRANSMITTERS, AND PHOSPHODIESTERASE INHIBITORS IN THE GUINEA PIG ILEUM: A HYPOTHESIS ON THE MECHANISM OF ACTION OF NARCOTICS

GINTZLER, Alan Richard, Ph.D.
New York University, 1974

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Inhibition of the electrically-induced contractions of the guinea pig ileum has been shown to be a reliable index to the relative potency of various narcotic analgesics. This property suggests that this preparation might be useful in attempts to elucidate the mechanisms by which morphine induces analgesia in the CNS. In light of the inhibitory effects of 5-HT on the ileum and its interactions with morphine in other tissues, the effects of 5-HT on the inhibitory response of the ileum to morphine were studied. Concentrations of 5-HT ranging from 2×10^{-8} to 2×10^{-7}M can potentiate the inhibitory effects of morphine and vice versa; small concentrations of morphine (10^{-8}M) can potentiate the inhibitory response to 5-HT. Both of these effects can be abolished by washing. This potentiation is also observed with both nalorphine and methadone, and seems to be due to a specific interaction between 5-HT and narcotic analgesics. Similar concentrations of 5-HT have no effect on the inhibition produced by NE, and NE itself has no effect on the inhibition produced by morphine. LSD (0.1 μg/ml) can antagonize the inhibitory effects of 5-HT, but can also produce a marked potentiation of the response to morphine. The above suggests that 5-HT may play an essential role in the mechanism by which morphine induces analgesia in the CNS.

The interaction between 5-HT and morphine suggested that there might be a crossover point between the pathway that mediates some of the effects of 5-HT and that which mediates the inhibitory effects of morphine. It seemed that this crossover point might involve ATP, since it has been speculated that some of the inhibitory effects of 5-HT may involve the release of ATP.

There are striking similarities between ATP and morphine in: (a) the pharmacologic effects that each one produces on the gut by itself; (b) their ability to alter the inhibitory response of the gut to NE and 5-HT; and (c) the way their inhibitory effects are altered by tolazoline, 5-HT, and several PDE inhibitors. The effects of various PDE inhibitors strongly suggests that cAMP formation might be involved in the inhibitory effects of morphine.

This hypothesis is consistent with either of two mechanisms of action: (a) morphine may act to inhibit responses of the gut to field stimulation by releasing ATP or some of its derivatives, or (b) morphine might act by mimicking the effects of adenosine or ATP. Attempts to demonstrate a morphine-induced stereospecific release of ATP were unsuccessful. It thus seems most probable that morphine is itself mimicking the effects of adenosine to cause an increase in cAMP. It is suggested that the ATP-cAMP pathway that mediates the effects of purinergic transmission is probably the neurochemical pathway that mediates the effects of morphine.

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THE EFFECT OF DIURETICS ON BLOOD VESSELS: THE MECHANISM OF THE ANTIHYPERTENSIVE EFFECT AFTER LONG TERM ADMINISTRATION OF ORAL DIURETICS. [To obtain a microfiche copy please order directly from the National Library of Canada at Ottawa]

HART, Frederick Edward, Ph.D.
University of Toronto (Canada), 1973

The antihypertensive action in the initial stages of thiazide therapy can probably be explained by the diuretic effect, but this does not entirely explain the lowered blood pressure after long term administration as the plasma volume and sodium balance gradually return to their pretreatment levels. This study presents new data on vascular reactivity both 'in vitro' and 'in vivo' which may help to elucidate the hypotensive action of these diuretics. In addition, the effect of these diuretics on electrolytes in either vessels or psoas muscle was studied in three species in an attempt to explain the mechanism of action.

The present 'in vitro' results have shown that prolonged