Psychopharmacology 54, 313 – 314 (1977)

Psychopharmacology

Short Reports

Interaction Between Narcotic Antagonist (Naloxone) and Lysergic Acid Diethylamide (LSD) in the Rat

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Abstract. LSD administration in rats elicited a diphasic reaction consisting of a brief excitable period (up to 8 min) followed by a prolonged catalepsy (8 min – 1 h). While the cataleptic response was antagonized by a single injection of naloxone (given 30 min after LSD administration), pretreatment with naloxone shortened the excitable phase and potentiated the catalepsy.

Key words: LSD 'bad trip' – Rats – Cataleptic analgesia – Narcotic antagonist – Naloxone-LSD antagonism

The analgesic (Kast and Collins, 1964) hallucinogen lysergic acid diethylamide (LSD) and the class of narcotic analgesics of which morphine is prototypical share the phenylethylamine structural element (Fischer, 1974). The spatial disposition of the nitrogen atom and the aromatic nucleus of the phenylethylamine group in morphine has been shown by Jung et al. (1976) to be identical with that present in the narcotic antagonist cyclazocine and other synthetic analgesics. The phenylethylamine pattern is present not only in cyclazocine but also in naloxone, and it is of interest to note that the latter can block the LSD-like side effects of the former (Fink et al., 1971). Inasmuch as there is no known specific antagonist with which to treat LSD-induced 'bad trips,' this preliminary study sought to examine any possible antagonistic interaction between LSD and the narcotic antagonist naloxone.

MATERIALS AND METHODS

Experiments were performed on 16 Sprague-Dawley rats (8 male and 8 female) weighing between 280 and 320 g. Each experiment commenced at zero time (t_0) with an i.p. injection of 375 µg/kg LSD dissolved in saline. Naloxone-HCl was administered i.m. at a dose of 0.2 mg/kg known to elicit withdrawal in narcotic-dependent rats (Wei, 1973). Naloxone was administered either 5 min prior to t_0 (t_{-5}) or 30 min after the LSD injection (t_{30}). Naloxone controls were i.m. saline injections at t_{-5} or t_{30}, and LSD controls were saline injections at t_0. All behavioral observations were made in a 122-cm square open-field black box divided into four equal isolated compartments that were 46 cm deep. This arrangement, reported by us previously (Fertziger et al., 1974), facilitates comparative drug studies in freely moving rats. Observations were reported by individuals ignorant of the nature of treatment.

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RESULTS

At the dose levels described in this study LSD consistently elicited brief hyperactivity that changed in about 8 min to a hypoactive 'catalepsy' of about 1 h duration. During this state rats became unresponsive to the environment and to noxious stimulation (pinching); their eyes were wide open and their neuromuscular tone was such that their bodies could be 'shaped' into atypical positions. This behavior was strikingly similar to the morphine- or methadone-induced catalepsy described by Ahtee and Kaariainen (1973), Ayhan and Randrup (1972), and Fog (1970), and the ketamine-induced 'cataleptic anaesthesia' reported by Winters et al. (1973). Rats generally remained fixed in a corner, heads up, eyes wide open, and feet seemingly fixed to the floor.

Pretreatment (t_{-5}) with naloxone tended to shorten the initial hyperexcitability and prolong and intensify the LSD-induced 'catalepsy,' but the naloxone injections at t_{30} reversed much of the LSD 'catalepsy.' Within minutes of these injections, the immobile rats once again became exploratory and active and soon resembled the LSD-control rats whose behavior remained unremarkable throughout the duration of the experiment. Saline injection at t_{30} did not alter the LSD-induced 'catalepsy.' This naloxone antagonism

is similar to the naloxone antagonism of methadone-induced 'catalepsy' reported by Ahtee (1974).

DISCUSSION

Since low doses of LSD can induce analgesia in man (Kast and Collins, 1964; Kuromaru et al., 1967), the higher LSD dose administered to our rats should intensify the analgesic response. Only the post-LSD administration of naloxone antagonized LSD-induced 'catalepsy' and presumably the concurrent analgesia; therefore, this preliminary report is compatible with the notion that LSD may set free analgesic endorphines (enkephalins), the latter of which are known to be counteracted by naloxone (Belluzzi et al., 1976). Whether this hypothesized LSD-induced enkephalin-naloxone interaction is related to the partial structural similarity between LSD, morphine, enkephalin, and naloxone is a matter of speculation. The literature implies that 'analgesic bliss' may be induced by hallucinogens, such as psilocybin, LSD (Kuromaru et al., 1967), ketamine, the N-substituted isostere of Δ^9-THC (Villarreal et al., 1974), methoxylated amphetamines, and morphine and its antagonists (Fischer, 1974). The analgesic and/or anesthetic effect of all these compounds may be a function of the endorphine concentration, which they are able to displace through interaction with common 'hallucinogenic' receptors.

In addition to being a narcotic antagonist, naloxone possesses other 'fatigue reversing' pharmacological properties (VanNueten et al., 1976) that may mask cataleptic analgesia. In any case, the present preliminary results imply that naloxone may counteract LSD-induced analgesia in humans.

Acknowledgements. LSD and naloxone were obtained through the courtesy of Ms. Jackie Bryant, Program Support Section, Center for Studies of Narcotic and Drug Abuse, N.I.D.A., Rockville, Maryland and Endo Laboratories, Garden City, New York, respectively.

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Received January 6, 1977