Pharmacology Biochemistry & Behavior, Vol. 19, pp. 985–986, 1983. © Ankho International Inc. Printed in the U.S.A.

The Suppression of Ethanol Self Injection by Buprenorphine

ANN MARTIN, RUDY PILOTTO, GEORGE SINGER[1] AND TIAN P. S. OEI

Department of Psychology and Brain-Behaviour Research Institute
La Trobe University, Bundoora Australia 3083

Received 6 October 1982

MARTIN, A., R. PILOTTO, G. SINGER AND T. P. S. OEI. *The suppression of ethanol self injection by buprenorphine.* PHARMACOL BIOCHEM BEHAV 19(6) 985–986, 1983.—The schedule induced self-injection procedure was used to establish ethanol self-injection in 16 rats. Pretreatment with an injection of 0.3 mg/kg buprenorphine significantly reduced ethanol self-injection in a group of 8 rats. This effect was not found in a second group of 8 rats which received saline pretreatment. The findings provide support for an involvement of buprenorphine, in ethanol self-injection, which cannot be explained in terms of opiate induced shifts in taste preference. From the present data it cannot be determined whether the agonist or antagonist opiate properties of buprenorphine cause the blocking effect.

Schedule induced self injection Ethanol Buprenorphine

RECENT evidence indicates that there is an action of opiates on ethanol related behaviours [2]. This suggestion is supported by reports that injections of morphine suppress the volitional consumption of alcohol by rats [10] and mice [4]. Opiate antagonists have also been reported to suppress volitional intake; significant decreases in ethanol self injections by monkeys following pre-treatment with naloxone have been reported [1]. Other studies show increased voluntary ethanol consumption in hamsters [7] and a preference shift towards alcohol induced by very low doses of naloxone or naltrexone in mice. These contradictory findings may be the result of methodological differences or reflect changes in the agonist/antagonist ratio with changing dose levels.

Buprenorphine is a stereospecific opiate agonist/antagonist which combines the blocking action of naloxone with some of the analgesic properties of morphine [6], and which has been used to suppress heroin self administration in humans without causing withdrawal symptoms or dependency [8]. It has been reported that buprenorphine solutions are self administered by monkeys, which suggests that buprenorphine also has reinforcing properties.

The aim of the present study was to explore the effects of buprenorphine pretreatment on the maintenance of ethanol self injection.

METHOD

Subjects

Sixteen experimentally naive male Long Evans rats, weighing between 300 and 350 g were used. Rats were housed individually in wire mesh cages on a 12 hr light/12 hr dark cycle with water available ad lib. Rats were weight reduced and maintained at 80% of free-feeding body weight (FFBW) by restricting food intake.

Apparatus

The testing chambers were modified operant boxes (35×32×32 cm) constructed from clear Plexiglas, with a food dispensing unit and plastic lever situated 3 cm and 5 cm respectively above the floor. The lever triggered the delivery of 0.065 ml of ethanol via an infusion pump which incorporated a five second delay between subsequent bar presses and drug delivery. An event recorder attached to the infusion pump provided a cumulative record of the number of bar presses and infusions. Noyes food pellets (45 mg) were delivered throughout the experiment on a one minute fixed time schedule (FT60).

Drugs

Ethyl ethanol solution (99.5%) (CSR Chemicals) was prepared for intravenous injection by dilution with 0.9% saline solution to a concentration of 19.9%. This provided a dose level of 0.05 ml per infusion. The choice of ethanol concentration and dose per infusion was based on evidence previously reported by Oei and Singer [7] and Smith, Oei, Ng and Armstrong [10]. Buprenorphine was diluted with 0.9% sterile saline giving a dose level of 0.3 mg/kg. The drug was injected intraperitoneally (IP). The anaesthetic used during surgery was sodium pentobarbitol, at a dose of 60 mg/kg injected IP.

Procedure

The animals were weighed, anaesthetised and surgically implanted with a polyethylene catheter in the jugular vein (SP28). The catheters were supported by a lightweight harness which allowed relatively unrestricted movement.

Following a 2 to 3 day recovery period and random assignment to experimental treatments, animals were tested

[1]Requests for reprints should be addressed to G. Singer.

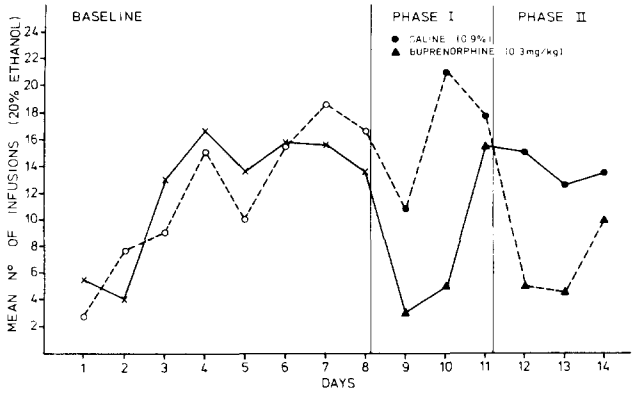

FIG. 1. Mean number of ethanol infusions for animals during baseline and treatment phases.

over three consecutive phases. Phase 1 was an 8 day acquisition phase. Phase 2 commenced after the acquisition phase and lasted for three days. During this phase rats assigned to group 1 received an IP injection of buprenorphine 2 hours prior to testing, while group 2 rats were injected with an equivalent amount of the saline. For each of the 3 days in phase 3, rats in group 2 received IP buprenorphine injections and group 1 rats the saline injection. All rats were tested for an hour each day at the same time of day.

RESULTS AND DISCUSSION

The mean number of ethanol infusions over the 14 days making up the 3 phases are presented in Fig. 1. A three way analysis of variance (ANOVA) with 3 repeated measures on the last 2 phases were carried out in order to determine main effects for drug conditions (DC), phases (PH) and days (D) and interactions between them. The results show that the only significant main effect was between buprenorphine and saline (DC), $F(1,14)=5.233$, $p<0.05$, showing that pretreatment with buprenorphine suppresses ethanol intake (Fig. 1). There were no significant interactions.

The results show that 0.3 mg/kg buprenorphine significantly inhibits the maintenance of ethanol self injection. It has been reported [3] that buprenorphine at doses of 0.3 mg/kg and 3.0 mg/kg increases activity levels therefore the effects shown in this experiment are not likely to be the result of diminished activity induced by the drug. Similarly, since ethanol self administration was through intravenous catheters, changes in taste sensitivity can be ruled out. It is possible that the reinforcing effect of buprenorphine shown in monkeys [5] is due to a common reinforcement mechanism, alternatively the effect could be at the receptor level, through a direct blockade of receptors involved in ethanol intake.

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