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Self-Administration of Ketocyclazocine and Ethylketocyclazocine by the Rat[1]

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YOUNG, G. A. AND N. KHAZAN. *Self-administration of ketocyclazocine and ethylketocyclazocine by the rat.* PHARMACOL BIOCHEM BEHAV 19(4) 711–713, 1983.—The purpose of the study was to assess possible substitution of either ketocyclazocine or ethylketocyclazocine for morphine in rats maintaining their own dependence by self-administration. Rats were prepared with indwelling IV cannulae, made tolerant to and physically dependent on morphine, then trained to lever press for morphine self-injections on a fixed ratio (FR) schedule of reinforcement. When either ketocyclazocine or ethylketocyclazocine was substituted for morphine, rats self-administered single injections of these kappa opioid agonists at relatively evenly spaced intervals over a 24-hr period. These self-injection patterns continued for up to at least 15 consecutive days. Substitution of saline for the kappa opioid agonists did not result in the emergence of a morphine-like abstinence syndrome. Differences in extent and intensity of withdrawal between morphine and these kappa opioid agonists indicate the involvement of separate receptor populations in the process of dependence on morphine and these kappa opioid agonists.

Ketocyclazocine Ethylketocyclazocine Physical dependence Self-administration

MARTIN and his colleagues originally proposed, based upon *in vivo* findings of acute and chronic opioid effects on neurophysiological parameters in the chronic spinal dog preparation, that selective opioid agonists activate different populations of opioid receptors [3,8]. Since then, many additional differential effects of selective mu, kappa and sigma opioid agonists on neurophysiological, behavioral and biochemical parameters have been delineated.

For example, in studies of the effects of various opioids on flurothyl-induced seizures in the rat, morphine (mu agonist) and related opioids had dose-related anticonvulsant effects that were antagonized by naloxone [2]. Tolerance developed to these morphine-induced anticonvulsant effects. In contrast, neither ketocyclazocine nor ethylketocyclazocine (kappa agonists) and related opioids had any clear effect on flurothyl-induced seizures thresholds. Furthermore, SKF-10,047 (N-allyl-normetazocine, sigma agonist) had a dose-related anticonvulsant effect like that by morphine, but, in contrast to morphine, no tolerance developed to this effect and naloxone was ineffective as an antagonist, even at a 10 mg/kg dose.

In studies in which both cortical electroencephalographic (EEG) activity and behavior were assessed, morphine, ketocyclazocine and ethylketocyclazocine were reported to produce a similar "EEG-behavior dissociation" in the dog [10]. However, morphine reportedly increased the amount of sleep and decreased temperature, heart rate and respiratory rate; while ketocyclazocine and ethylketocyclazocine had no effect on sleep and increased temperature, heart rate and respiratory rate. The morphine-induced effects were reported to be more sensitive to naloxone antagonism than those of either ketocyclazocine or ethylketocyclazocine. Elsewhere, in the rat both morphine and ethylketocyclazocine produced similar biphasic EEG and behavioral profiles [13]. In this case, the ethylketocylcazocine-induced effect was found to be more sensitive to naloxone antagonism than the morphine-induced biphasic effect.

In our studies of the effects of mu, kappa and sigma opioid agonists on cortical EEG and EEG power spectra in the rat, we found differential dose-related neuropharmacological effects [18,19]. Morphine, intravenously administered to freely-moving rats, produced high-voltage cortical EEG bursts associated with increases in EEG spectral power in the zero to 10 Hz range. Ketocyclazocine produced high-voltage cortical EEG bursts associated with a predominant spectral peak in the 5–8 Hz band. SKF-10,047 produced desynchronized cortical EEG along with frequent theta wave activity; associated EEG power spectra consisted of the least power, peaking at about 7.5 Hz. Furthermore, the (−) enantiomers of methadone (mu agonist) and ketocyclazocine were active, producing EEG and power spectral effects qualitatively similar to those produced by the respective racemic mixtures. The (+) enantiomers were found to be inactive. The (+) enantiomer of SKF-10,047, however, produced behavioral changes reminiscent of those produced by psychomimetic agents such as dimethyl- or diethyltryptamine.

One property of kappa opioid agonists that has not been clearly delineated and compared is their possible abuse potential. It has been reported that ketocyclazocine and ethyl-

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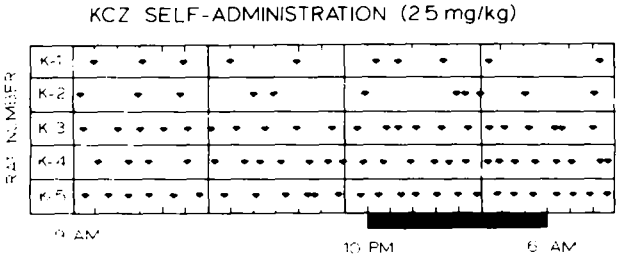

FIG. 1. Ketocyclazocine self-injection distributions (filled arrows) over a 24-hr period in five individual rats. Lights-off period is indicated by the dark horizontal bar.

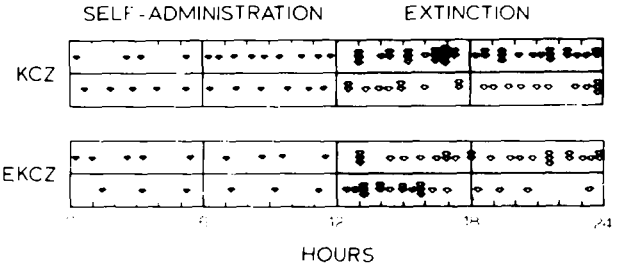

FIG. 2. Ketocyclazocine and ethylketocyclazocine self-injection distributions (filled arrows) and subsequent extinction (shaded areas) during saline substitution (open arrows). Data are shown over a 24-hr period for four individual rats.

ketocyclazocine are not self-administered by the monkey [4, 16, 17]. In contrast, self-administration of ethylketocyclazocine by the rat has been observed (Weeks and Collins, personal communication). In the present study, we studied possible substitution of either ketocyclazocine or ethylketocyclazocine for morphine in rats maintaining their own dependence by self-administration.

METHOD

Ten female Sprague-Dawley rats (250–300 g) were used. For drug injections, a silicone rubber cannula was implanted under ketamine anesthesia (100–150 mg/kg, IP) into the right external jugular vein [14,15]. Throughout the study, each rat was maintained in an individual cage that was equipped with a response lever, and a swivel with a feed-through cannula for drug administration [5,7]. Lighting conditions consisted of a timer-regulated period of darkness from 10 p.m. to 6 a.m. Lever presses and drug injections were recorded on an Esterline-Angus event recorder. The drugs used were: morphine sulfate, ketocyclazocine base and ethylketocyclazocine methanesulfonate. Morphine sulfate was dissolved in isotonic saline (0.9%), and a 0.1 ml volume was delivered by a Harvard infusion pump over six sec for intravenous drug administration. Ketocyclazocine base was dissolved in a small amount of glacial acetic acid and brought up to a concentration of 2.5 mg/kg with isotonic saline. Ethylketocyclazocine methanesulfonate was dissolved in a small amount of 0.5 N NaOH and brought up to a concentration of 2.5 mg/ml with isotonic saline. Doses are expressed as the salt.

All ten rats were first made tolerant to and physically dependent on morphine by a series of automatic intravenous injections delivered every hour. On the first day, rats received a dose of 1.25 mg/kg/hr of morphine. The dose was then increased to 2.5, 5.0, 10.0 and 20.0 mg/kg/hr on successive days. Each rat was then trained to lever press in order to receive morphine on a fixed ratio (FR) schedule of reinforcement. A FR of one lever press was initially required per injection, and the FR was gradually increased to 10 over a period of several days. After the rats had stabilized self-administration patterns for morphine (10 mg/kg/injection), either ketocyclazocine (2.5 mg/kg/injection) or ethylketocyclazocine (2.5 mg/kg/injection) was substituted for morphine in two groups of five rats each. The 2.5 mg/kg dose of kappa opioid agonists was selected because our acute EEG studies previously demonstrated that 10 mg/kg of morphine and 2.5 mg/kg of ketocyclazocine produced similar increases in EEG spectral power [19]. Rats had access to ketocyclazocine or ethylketocyclazocine for self-administration from five to fifteen days. After several days of ketocyclazocine or ethylketocyclazocine self-administration, saline was substituted for the opioid agonist.

RESULTS

Upon substitution of ketocyclazocine for morphine, self-injections continued. Distributions of ketocyclazocine self-injections (2.5 mg/kg/injection) during the third or fourth day after substitution for morphine are shown in Fig. 1 for five individual rats. For each rat, self-injections were relatively evenly spaced over the 24-hr period. These rats took an average of 19.0±2.8 (mean±s.e.m.) self-injections during the indicated 24-hr period. (The average morphine intake of these same rats on the last day before ketocyclazocine substitution was 12.8± 1.9 self-injections). These self-injection patterns continued for up to 15 days in rats given access to ketocyclazocine for that span of time. Rats displayed similar patterns of self-administration when ethylketocyclazocine (2.5 mg/kg/injection) was substituted for morphine.

Effects of saline substitution for ketocyclazocine or ethylketocyclazocine upon self-injection patterns are shown for four representative rats in Fig. 2. Saline self-injection rates increased over opioid self-injection rates during the first few hours of extinction. However, saline substitution did not result in the emergence of a morphine-like abstinence syndrome. Symptoms such as diarrhea, ptosis and wet-dog shakes were minimal compared to those seen during morphine abstinence in our laboratory. Slow-wave sleep and rapid eye movement sleep were not disrupted.

DISCUSSION

The present study clearly demonstrated that ketocyclazocine and ethylketocyclazocine are self-administered by the rat. Self-injections of either of these kappa opioid agonists were self-administered at relatively evenly spaced intervals throughout a 24-hr period. This self-injection pattern was sustained for up to at least 15 consecutive days. Similar self-injection patterns have been previously demonstrated in our laboratory during the self-administration of morphine, methadone, l-alpha-acetylmethadol (LAAM), nor-LAAM, dinor-LAAM, nalbuphine, butorphanol and pentazocine [7, 9, 11, 12, 20]. Thus, at a behavioral level in the rat, kappa opioid self-administration does not differ from the self-administration of several opioids, including selective mu opioid agonists. In marked contrast, it has been reported that monkeys do not self-administer kappa opioid agonists

[4, 16, 17]. This is particularly puzzling since dynorphin-(1–13), a purported endogenous kappa agonist, has been found to substitute for morphine in morphine-dependent monkeys [1]. Likewise, we have found that both dynorphin-(1–13) and D-ala^2-dynorphin-(1–11) substitute for morphine in morphine-dependent rats.

Our present results demonstrated that both ketocyclazocine and ethylketocyclazocine substituted for morphine during self-administration. However, when saline was substituted for these kappa opioid agonists, only a mild abstinence syndrome was evident. The question is raised as to whether the kappa opioid agonists and morphine are producing their reinforcing effects in sustaining self-administration via the same receptor populations. Since morphine abstinence is associated with severe withdrawal symptoms and ketocyclazocine and ethylketocyclazocine are not, the involvement of separate receptor populations in the process of dependence on morphine and these kappa opioid agonists is indicated. In conclusion, both a mu and two kappa agonists exhibit an analogous reinforcing property in the rat. However, the degree of physical dependence and the intensity of withdrawal differ, being higher with the mu agonist and lower with the kappa agonists.

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