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Naloxone Antagonism of the Thermoregulatory Effects of Phencyclidine

Abstract. *Phencyclidine elicits hyperthermia at low doses and hypothermia at high doses in rats. Naloxone antagonizes both effects. Phencyclidine's effects on thermoregulation are probably mediated by an interaction with a mu opiate receptor.*

An understanding of the pharmacological properties of phencyclidine (PCP) has become important due to the increased incidence of PCP abuse. Recent studies have focused on characteristics that PCP seems to share with the psychotomimetic opioids. Of special interest have been the observations that in rats and squirrel monkeys trained to discriminate PCP from saline the PCP response can be generalized to *N*-allylnormetazocine and that neither effect is antagonized by naloxone (*1*). *N*-Allylnormetazocine is a benzomorphan opioid that is considered the prototypical agonist of the putative sigma opiate receptor (*2*). Thus PCP may also be a sigma opiate agonist, a suggestion supported by evidence of a shared binding site with sigma opiate ligands in rat brain (*3*). There is also evidence, however, that PCP binds to mu opiate receptors sensitive to morphine and naloxone (*4*). We report here that PCP elicits biphasic changes in body temperature that are readily antagonized by naloxone.

Baseline temperatures of female Sprague-Dawley rats (220 to 250 g) were determined rectally with an electronic digital thermometer (IVAC Corp.) accurate to ± 0.1°C (*5*). In groups of three, each rat then received two intraperitoneal injections: one of PCP hydrochloride (0.625 to 40 mg/kg) and one of saline (1 ml/kg), one of PCP and one of naloxone hydrochloride (1.0 mg/kg), one of naloxone and one of saline, or two of saline. Rectal temperatures were again determined 15, 30, 45, and 60 minutes later. Each animal was used for only one treatment on one occasion. Ambient temperature was maintained at 22°C.

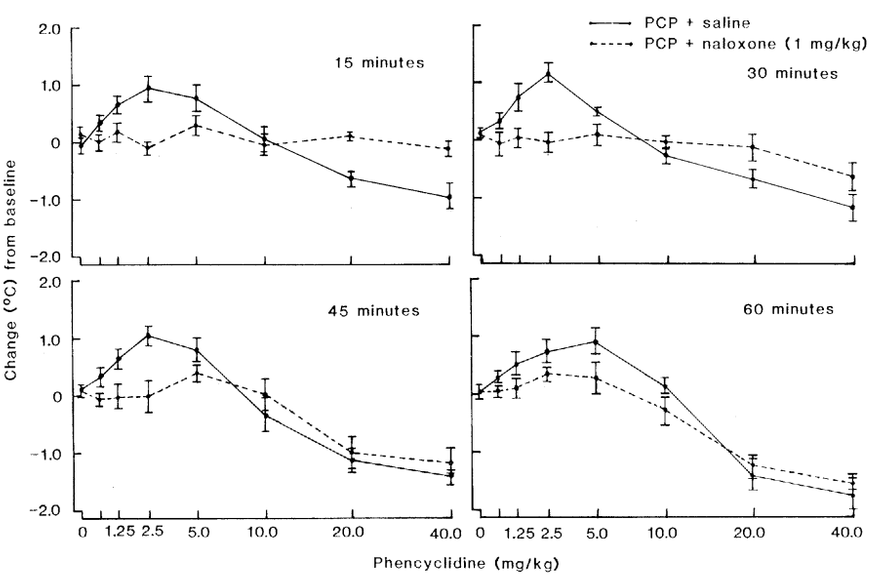

Fig. 1. Time-dependent effects of PCP and PCP plus naloxone on body temperature in rats. Values are means ± standard errors for three experiments.

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Figure 1 shows the results for each interval after treatment. A two-way analysis of variance, with the dose of PCP and the saline or naloxone treatment as the main factors, was conducted for each time point. Both main effects and their interaction were significant ($P < .05$) at 15, 30, and 45 minutes; only the main effect of PCP was significant at 60 minutes. Paired *t*-tests between baseline temperatures and temperatures after treatment reveal that, at all time points, PCP elicited significant hyperthermia at low doses (0.625 to 5.0 mg/kg) and significant hypothermia at high doses (20.0 to 40.0 mg/kg) ($P < .05$). The combination of PCP and naloxone resulted in no significant changes in temperature after 15 minutes and in significant ($P < .05$) hypothermia 30 and 45 minutes after high doses of PCP (40.0 mg/kg and 20.0 and 40.0 mg/kg, respectively). After 60 minutes the effects of PCP plus naloxone did not differ significantly from those of PCP plus saline. Thus naloxone completely antagonized PCP for 15 minutes, after which this effect gradually disappeared.

Reversal of PCP's effects was also demonstrated. After baseline temperatures were determined in eight additional rats, four were administered a hyperthermic dose of PCP (2.5 mg/kg) and four were given a hypothermic dose (20.0 mg/kg). Rectal temperatures were recorded at 15 minutes, and immediately thereafter all the rats were administered naloxone (1 mg/kg). Temperatures were measured again after 15 minutes. The effects of PCP administered alone at doses of 2.5 and 20.0 mg/kg are greater after 30 minutes than after 15 minutes (Fig. 1). In the present instance, however, whereas the hyperthermic and hypothermic effects were readily apparent after 15 minutes, the subsequent administration of naloxone reversed these effects in another 15 minutes. Mean changes in temperature from baseline 15 minutes after the naloxone injections were $0.03° \pm 0.08°C$ for the rats that received 2.5 mg of PCP per kilogram and $-0.15° \pm 0.13°C$ for the rats that received 20.0 mg of PCP per kilogram.

In previous investigations interactions of naloxone with PCP have been absent or negligible (*1*, *6*). The present data, in contrast, indicate that PCP's effects on at least one physiological system are sensitive to naloxone. The gradual waning of the naloxone antagonism after 15 minutes and the reversal of PCP's effects make it very unlikely that the present interaction is in any way attributable to alterations in PCP's pharmacokinetics. It is of interest that morphine also elicits dose-dependent hyperthermia and hypothermia in rats (*7*) and that, as with PCP, both effects can be antagonized by naloxone. Indeed, the sensitivity of PCP to antagonism by naloxone appears similar to the reported sensitivity of morphine to naloxone antagonism (*8*). Antagonism at sigma receptors requires higher doses of naloxone than antagonism at mu receptors (*2*), and naloxone does not appear to antagonize temperature responses elicited by *N*-allylnormetazocine (*9*). Thus, it is likely that PCP and naloxone interact at mu opiate receptors in brain areas controlling thermoregulatory processes.

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Characterization of Estrogen-Concentrating Hypothalamic Neurons by Their Axonal Projections

Abstract. *A method combining steroid autoradiography and fluorescent dye retrograde neuroanatomical tracing has been devised. This method makes it possible to demonstrate that some estrogen-concentrating cells in the ventrolateral subdivision of the ventromedial nucleus of the rat hypothalamus are neurons that send axons to the dorsal midbrain. Other cells only concentrate estrogen or only project to the midbrain. Estrogen-concentrating neurons in the ventromedial hypothalamus that project to the dorsal midbrain are likely to transmit hormone-influenced signals that regulate circuits for reproductive or other behaviors or autonomic functions.*

Gonadal steroid hormones exert powerful effects on the brain, regulating sexual behaviors and gonadotropin release, probably via cells binding gonadal steroid hormones. Autoradiography has made it possible to demonstrate these hormones in the hypothalamus and limbic system of all the vertebrates examined (*1*) including the rat (*2*).

Large numbers of estradiol-concentrating cells have been demonstrated in the ventrolateral subdivision of the ventromedial nucleus of the rat through the use of steroid autoradiographic methods (*2*). The horseradish peroxidase retrograde tracing method revealed that large numbers of neurons in the ventromedial nucleus, particularly in the anterior and ventrolateral subdivisions, sent their axonal projections to the dorsal midbrain (*3*). Cellular estradiol concentration in an area known to project to the dorsal midbrain prompted us to ask whether any estradiol-concentrating cells in the ventromedial nucleus are neurons that project to the midbrain.

Primuline, true blue, and granular blue are fluorescent dyes which are transported retrogradely through axons to the neuronal soma (*4*). Arnold (*5*) has studied the efferent projections of certain dihydrotestosterone concentrating neurons in the bird telencephalon by a combined method with primuline in unfixed tissue. We have used these retrogradely transported fluorescent dyes combined with steroid autoradiographic procedures to demonstrate the efferent projections of estradiol-concentrating neurons in the ventromedial nucleus of the rat.

Seven ovariectomized 2-month-old Long-Evans (Charles River Laboratories) female rats (body weight, 150 to 200 g) received dorsal midbrain injections of the fluorescent dye primuline (ICN Pharmaceuticals) (*6*). After allow-

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