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Neuropeptide-Y exerts antidepressant-like effects in the forced swim test in rats

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Abstract

The effects of neuropeptide-Y were examined in the forced swim model of depression in rats. Following a 15-min preswim, four groups of rats were given three intracerebroventricular (i.c.v.) injections of neuropeptide-Y (0.5, 5, or 10 μg) or saline over a 24-h period. Several behaviors were subsequently measured during a 5-min forced swim. Neuropeptide-Y treatment dose dependently increased swimming and decreased immobility. The pattern of results is consistent with that produced by serotonergic antidepressant drugs in this model.

Keywords: Neuropeptide-Y; Stress; Depression

Neuropeptide-Y is an abundant and highly conserved neurotransmitter that regulates emotional behavior, cognition, feeding, circadian rhythms, and autonomic and endocrine functions (Wahlestedt and Heilig, 1995). Previous clinical studies implicate neuropeptide-Y dysfunction in some forms of depression. Several studies have reported decreased neuropeptide-Y levels in the cerebrospinal fluid (Heilig and Widerlov, 1990) and plasma (Nilsson et al., 1996) of depressed patients compared to healthy controls. Levels of neuropeptide-Y correlate negatively with anxiety scores in depressed patients (Heilig and Widerlov, 1990), suggesting that individuals with low levels of neuropeptide-Y may be predisposed to anxiety-related or stress-induced depression.

Previous experiments in rats have demonstrated that chronic antidepressant treatment and electroconvulsive stimulation increase neuropeptide-Y gene expression and decrease neuropeptide-Y Y_2 receptor densities in distinct brain regions in rats (Heilig et al., 1988; Widdowson and Halaris, 1991). These results suggest that antidepressants may exert some of their therapeutic effects through upregulation of endogenous neuropeptide-Y. Neuropeptide-Y also produces antidepressant-like effects in the olfactory bulbectomized rat model of depression (Song et al., 1996). These findings suggest antidepressant properties of both endogenous and exogenous neuropeptide-Y.

The present experiment studied the effect of intracerebroventricular (i.c.v.) administration of neuropeptide-Y in the Porsolt forced swim test in rats, which is a reliable tool for screening antidepressant drugs (Porsolt et al., 1977). The experiments provide a novel test of the hypothesis that central administration of neuropeptide-Y would produce antidepressant-like effects in the forced swim model.

Forty-one male Sprague–Dawley rats (234–284 g at the time of testing) served as subjects. Rats were individually housed with free access to food and water in an environmentally regulated vivarium maintained on a 12-h light cycle. Following 1 week of habituation to the vivarium, rats were anesthetized with halothane, placed in a stereotactic frame, and guide cannulae were implanted unilaterally above the right lateral ventricle at the following coordinates from bregma: posterior: 1.0 mm, ventral: 3.0 mm, lateral 1.5 mm. Cannulae were secured with dental acrylic surrounding jewelers screws affixed to the skull. After a 7-day recovery period the rats were placed in a 19-cm-diameter cylinder filled with 22°C water to a depth of 28 cm for 15 min. Rat neuropeptide-Y (RBI, Natick, MA, USA) was dissolved in 0.9% saline (pH = 7.4). Rats received i.c.v. injections of neuropeptide-Y (0.1, 1, or 2 μg/μl) or saline in 5-μl volumes through an injector extending 2 mm beyond the cannula tip. Rats were injected immediately, 8 and 23 h following the preswim. Twenty-four hours after the first injection, the rats were placed

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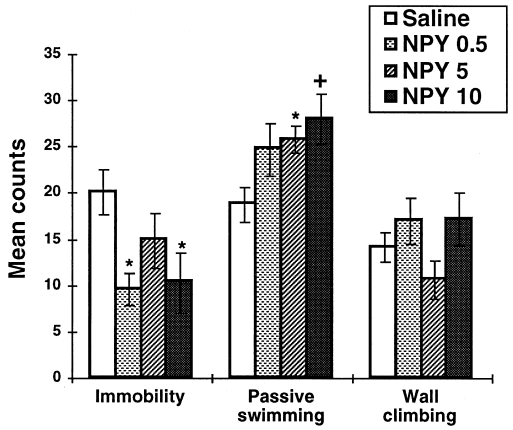

Fig. 1. Rats were placed in a cylinder of water for 15 min. Rats then received three i.c.v. injections of neuropeptide-Y (NPY: 0.5 μg, $n = 10$; 5 μg, $n = 9$; or 10 μg, $n = 10$) or saline ($n = 12$) delivered immediately, 8 h, and 23 h following the preswim. Rats were replaced in the swim apparatus 1 h after the final injection and the incidence of several behaviors was recorded every 5 s for 5 min. Data are presented as mean ± standard error. Significant differences from saline: $^{*}p < 0.05$, $+\ p < 0.01$.

back into the water for 5 min, and their behavior was recorded every 5 s (Porsolt et al., 1977). Behavior was divided into five categories: immobility (forepaws immobile), passive swimming (forepaws moving underwater), active swimming (forepaws breaking the water's surface), wall climbing, and diving. All behavioral testing was conducted during the first 6 h of the light phase. The data were analyzed by analysis of variance (ANOVA) with least squares difference post hoc correction. All procedures were reviewed and approved by the University of Georgia Animal Care and Use Committee and followed the Guide for the Care and Use of Laboratory Animals (National Research Council).

Cannula placement and function were verified within 1 week of testing. Rats were placed in a CO_2 chamber until unconscious, injected i.c.v. with 5 μl of fast green dye (2 mg/ml), and decapitated. Brains were dissected to ensure the dye had reached the ventricles. No subjects were excluded from the data analysis because of improper cannula placement.

ANOVA revealed a significant difference between groups in immobility ($F(3,37) = 4.77,\ P < 0.01$) and passive swimming ($F(3,37) = 3.25,\ P < 0.05$) during the forced swim test (see Fig. 1). Post hoc tests indicated that the low-dose neuropeptide-Y (0.5 μg) and high-dose neuropeptide-Y (10 μg) groups showed significantly less immobility during the swim test than the saline group ($P < 0.05$). The middle-dose neuropeptide-Y (5 μg) and high-dose neuropeptide-Y groups showed significantly more passive swimming than the saline group ($P < 0.05$; $P < 0.01$, respectively). Neuropeptide-Y treatment did not significantly influence active swimming, diving, or wall climbing.

The present results support the hypothesis that neuropeptide-Y exerts antidepressant effects. The action of neuropeptide-Y in decreasing immobility and increasing swimming without affecting wall climbing resembles the action of selective serotonin reuptake inhibitors in the forced swim test (Lucki, 1997). This pattern differs from that produced by antidepressants primarily targeting norepinephrine systems, suggesting that neuropeptide-Y may mediate its effects primarily through the enhancement of serotonergic transmission. Further experiments with selective antagonists are required to identify the neuropeptide-Y receptor subtype that mediates the antidepressant-like effects of neuropeptide-Y.

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References

Heilig, M., Wahlestedt, C., Ekman, R., Widerlov, E., 1988. Antidepressant drugs increase the concentration of neuropeptide Y-like immunoreactivity in the rats brain. Eur. J. Pharmacol. 147, 456–467.

Heilig, M., Widerlov, E., 1990. Neuropeptide Y: an overview of central distribution, functional aspects, and possible involvement in neuropsychiatric illnesses. Acta. Psychiatr. Scand. 82, 95–114.

Lucki, I., 1997. The forced swimming test as a model for core and component behavioral effects of antidepressant drugs. Behav. Pharmacol. 8, 523–532.

Nilsson, C., Karlsson, G., Blennow, K., Heilig, M., Ekman, R., 1996. Differences in the neuropeptide Y-like immunoreactivity of the plasma and platelets of human volunteers and depressed patients. Peptides 17, 359–362.

Porsolt, R.D., Anton, G., Blavet, N., Jalfre, M., 1977. Behavioral despair in rats: a new model sensitive to antidepressant treatments. Eur. J. Pharmacol. 47, 379–391.

Song, C., Early, B., Leonard, B.E., 1996. The effects of central administration of neuropeptide Y on behavior, neurotransmitter, and immune functions in the olfactory bulbectomized rat model of depression. Brain, Behav., Immun. 10, 1–16.

Wahlestedt, C., Heilig, M., 1995. Neuropeptide Y and related peptides. In: Bloom, F.E., Kupfer, D.J. (Eds.), Psychopharmacology: The Fourth Generation of Progress. Raven Press, New York, NY, pp. 543–551.

Widdowson, P.S., Halaris, A.E., 1991. Chronic desipramine treatment reduces regional neuropeptide Y binding to Y_2-type receptors in rat brain. Brain Res. 539, 196–202.