# Anxiolytic-Like Action of Neuropeptide Y: Mediation by Y1 Receptors in Amygdala, and Dissociation from Food Intake Effects

*Markus Heilig, M.D., Ph.D, Sarah McLeod, Michelle Brot, Ph.D., Steven C. Heinrichs, Ph.D., Frederique Menzaghi, Ph.D., George F. Koob, Ph.D., and Karen T. Britton, M.D., Ph.D.*

*Evidence from animal and human studies suggests that neuropeptide Y (NPY) may be a potent endogenous anxiolytic. The anatomic structures mediating this action of the peptide remain unknown. Furthermore, in addition to its anxiolytic-like effects, intracerebroventricular administration of NPY induces food intake through hypothalamic mechanisms, making the anxiolytic-like action of the peptide more difficult to interpret. The purpose of this study was to examine the anatomic substrate for the effects of NPY on anxiety, and to characterize the NPY receptors mediating these effects. Intracerebroventricular injection of NPY produced increased food intake in free-feeding animals, and dose-dependent anticonflict/anxiolytic-like effects in an established animal model of anxiety, the Geller–Seifter punished responding test. In contrast, microinjection of NPY into the central nucleus of the amygdala did not increase food intake in free-feeding animals, did not affect unpunished lever pressing for food, but did reproduce the anticonflict/anxiolytic-like effect with high potency. The selective NPY-Y1 agonist, p[Leu$^{31}$,Pro$^{34}$]NPY was approximately equipotent with native NPY in the conflict paradigm, and markedly more potent than the Y2 agonist, NPY$_{13-36}$. Intrastriatal injections had no effect on conflict behavior. Thus, activation of Y1 receptors in the central nucleus of the amygdala produces effects similar to established anxiolytics without affecting food intake, suggesting that Y1-receptors in the amygdala may be a substrate for anxiolytic actions of NPY.*

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KEY WORDS: *Neuropeptide Y; Receptors; Amygdala; Stress; Anxiety; Depression*

Neuropeptide Y (NPY) (Tatemoto et al. 1982) is one of the most abundant peptide transmitters in the mammalian brain. In addition to numerous effects on endocrine and autonomic function, it produces striking behavioral effects after central administration. Among these, stimulation of food intake, and an anticonflict/anxiolytic-like action are prominent (for review see Heilig and Widerlöv 1990). The latter action of the peptide is particularly interesting in conjunction with reports that NPY may be involved in the pathophysiology of depressive and/or anxiety symptoms in humans (Widerlöv et al. 1988; Heilig and Widerlöv 1990; Widdowson et al. 1992).

The anxiolytic-like action of NPY has been observed in different animal models of anxiety, but has only been reported after intracerebroventricular (ICV) administration of the peptide (Heilig et al. 1989). Therefore, the anatomic structures mediating this action of NPY remain unknown. Furthermore, ICV administration of NPY is sufficient to increase food intake (Clark et al. 1984). Therefore, an increased appetitive drive could constitute a confounding factor when apparent anxiolytic-like effects of NPY are observed after ICV adminis-

From the Department of Neuropharmacology, The Scripps Research Institute, (MH, MB, SH, FM, GFK), La Jolla, California; and the Department of Psychiatry, San Diego Veterans' Administration Medical Center, and University of California at San Diego (SM, KTB), La Jolla, California.

Address correspondence to: Markus Heilig, M.D., Ph.D., Department of Psychiatry and Neurochemistry, University of Göteborg, Mölndals Sjukhus, S-431 80 Mölndal, Sweden.

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tration, in particular in tests that rely on measures of consummatory behaviors.

It has been established that hypothalamic structures mediate the effects of NPY on food intake (Stanley and Leibovitz 1985; Levine and Morley 1984). Conversely, the amygdaloid complex and in particular the central nucleus of the amygdala are known to be important for emotionality, and the central nucleus receives a dense NPY-ergic innervation (Chronwall et al. 1985; Zardetto-Smith and Gray 1990). The present study was undertaken to examine the question of whether orexigenic and anxiolytic-like effects of NPY can be anatomically dissociated, and to test the hypothesis that anxiolytic-like effects of NPY are produced in the amygdaloid complex. An established animal model of anxiety, the Geller–Seifter punished responding test (Pollard and Howard 1979) was used to assess anticonflict/anxiolytic-like effects. Food intake as well as conflict behavior were studied both after ICV injection of NPY and after microinjections into the central amygdaloid nucleus. Since a heterogeneity of central NPY receptors has been demonstrated (Wahlestedt et al. 1990; Aicher et al. 1991), selective ligands for NPY-Y1 and Y2 receptors were used to characterize the receptors involved in producing anxiolytic-like effects of NPY.

## MATERIALS AND METHODS

### Subjects

Male albino Wistar rats, weighing between 200 and 275 g at the start of the experiment were used. Animals were housed three per cage, in a light- and temperature-controlled environment. For operant training and testing, rats were food deprived to 85% of their free-feeding weight, and then maintained on 15 g food per day in addition to that earned during testing. The following groups of animals were used: ICV injections of NPY/conflict testing ($n$ = 32, also used for the tail-flick test; these data have been published as a part of another study [Heilig et al. 1992]); amygdala injections of NPY and analogs/conflict testing ($n$ = 30; these animals were used in three separate experimental trials; they were allowed at least 7 treatment-free days after each of these, and were rerandomized for each trial); striatum injections of NPY/conflict testing ($n$ = 15); ICV injections of NPY/food intake ($n$ = 16); and amygdala injections of NPY/food intake ($n$ = 16). All experimental procedures were approved by the animal ethics committee at the San Diego VA Medical Center.

### Surgical Procedure and Injections

Under halothane anesthesia, animals were stereotactically implanted with guide cannulas, which were secured to the skull using stainless-steel screws and acrylic cement, and were closed with obturators when not used. At least 10 days of recovery were allowed after surgery. For ICV experiments, 23-gauge guide cannulas aimed 1 mm dorsal to a planned injection site in the lateral cerebral ventricle were used (final coordinates: 0.6 mm posterior and 2.0 mm lateral to bregma, 4.2 mm ventral to skull surface; tooth bar at +5.0 mm); peptide or vehicle was injected over 1 minute through a 30-gauge injector connected to a Hamilton syringe in a volume of 5 µl. Conflict testing was started 60 minutes following injection. For amygdala injections, bilateral 26-gauge guides aimed 3.0 mm dorsal to the final injection site were used (2.3 mm posterior and 4.2 mm lateral to bregma, 8.1 ventral to skull surface; tooth bar at −3.3 mm), and injections were given over 3 minutes through a 33-gauge injector in a volume of 0.5 µl. Conflict testing was performed 15 minutes after injection of drug. For intrastriatal injections, the same procedure was used as for the amygdala experiments, but the final coordinates were 1.0 mm anterior and 3.0 mm lateral to bregma, 5.0 mm ventral to skull surface; tooth bar at −3.3 mm. For the site injections, injectors were inserted and left in place for 3 minutes 2 days prior to the first actual injection to minimize nonspecific injection artifacts upon subsequent injections. For ICV injections, correct placement was ensured by gravity injection of 5 µl saline prior to experiments. For site injections, coordinates were histologically verified.

### Conflict Test

Training and testing of animals was performed in sound-attenuated operant chambers (Coulbourn Instruments, Inc., Lehigh Valley, PA). Chambers were equipped with stainless-steel bar floors through which electric shock could be delivered. Animals were first trained to lever-press for 45 mg of Noyes food pellets on a continuous reinforcement schedule. They were subsequently switched to a random-interval 30-second reinforcement schedule, and finally trained on a multiple-schedule conflict test with incremental shock (Pollard and Howard 1979). The conflict test consisted of three components: a pure reward (unpunished) component, a time-out component, and a conflict (punished) component. Responses made during the reward component were reinforced on a random-interval 30-second schedule in a darkened chamber. The chamber was illuminated with a house light during the time-out component, and responses were not reinforced. The third component (conflict) was signaled by three flashing lights above the lever (1/sec) and responses were both rewarded with food and punished with footshocks on a continuous reinforcement schedule. Footshock consisted of a scrambled biphasic square-wave pro-

duced by a SGS-003 stimulator (BRS/LVE Division of Technical Services Inc., Laurel, MD). During the conflict component, shock was incremental in 0.15-mA steps to a maximum of 3.3 mA with delivery of every reinforcer.

A testing session consisted of a 5-minute reward period, a 2-minute time-out, and a 2-minute conflict period presented in succession, with this sequence repeated twice. Testing sessions were repeated on successive days, at the same time of day. For each animal, baseline responding during both unpunished and punished components of the test was determined over two to three sessions preceding the session during which drug effects were studied. For each subject, responding during the actual testing session (number of lever presses) was expressed as a percentage of this individual's baseline.

### Food Intake Experiments

In separate experiments, food intake was also measured in animals that had not undergone training for the conflict test. Free-feeding rats were placed one per cage, and habituated over 3 days to the introduction of a stainless-steel bowl containing a preweighed amount of Noyes precision pellets identical to those used in the conflict test. On the experimental day, sawdust was removed, the bowl was introduced, and remaining food (including spill) was weighed after 30 minutes, 1 hour, and 2 hours.

### Tail-Flick Test

A tail-flick test was performed immediately following the session during which effects of ICV NPY on conflict behavior had been studied. In this test, rats were held, and the tail was dipped 3.5 cm in 55°C water. The latency for the tail to flick was measured (Jansen, 1963).

### Statistical Analysis

*Food Intake.* The consumed amount of food at 30, 60, and 120 minutes was subjected to a two-way analysis of variance with respect to treatment, time, and the interaction between these two.

*Conflict Test.* The percent change of unpunished and punished responding versus pretrial baseline were separately subjected to one-way analysis of variance with respect to treatment. Multiple comparisons versus controls were performed using Dunnett's test.

### Chemicals

Porcine NPY, p[Leu$^{31}$,Pro$^{34}$]NPY and NPY$_{13\text{-}36}$ were all obtained from Bachem California (Torrance, CA).

## RESULTS

### Effects of Intracerebroventricular NPY

*Conflict Behavior.* In the conflict experiment, average baseline responding on the unpunished component was 213.4 ± 11.2 lever presses per session, and on the punished component 19.3 ± 0.8 lever presses per session (mean ± SEM). Neuropeptide Y (0.2 to 5.0 nmol) increased punished responding in a dose-dependent manner ($F[26,3] = 9.0$, $p < .001$). At the highest dose, punished responding was doubled ($p < .001$ vs. controls). A smaller increase in unpunished responding was also seen ($F[26,3] = 4.2$, $p < .015$), but was at most about 30%, and had already reached a plateau at 1.0 nmol (Fig. 1).

Very similar results were observed in a replication of this experiment in a separate group of rats. The doses of 0.2, 1.0 and 5.0 nmol of NPY (i.c.v.) produced a dose dependent increase in punished responding reaching a maximum of 161% of control, with no significant effect on unpunished responding.

*Food Intake.* NPY (2.0 nmol) produced a robust increase in food intake over 2 hours ($F[42,2,2,1] = 20.1$,

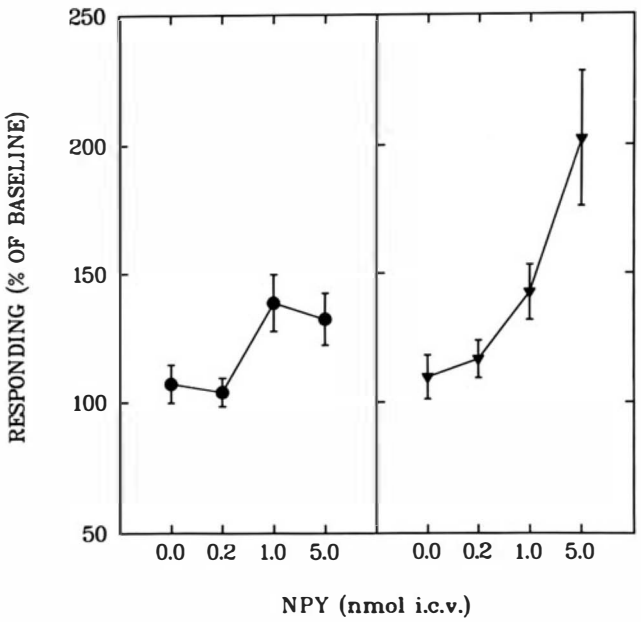


**Figure 1.** Dose-dependent increase of punished responding by NPY (0.2 to 5.0 nmol ICV) in the Geller–Seifter conflict test. Unpunished responding was only marginally affected. Responding, that is, the number of lever presses during the 2-minute punished, or the 5-minute unpunished test component, respectively, is expressed as the percentage of a baseline value obtained over two to three sessions preceding the session in which injections were made. Values are means of six to eight animals ± SEM. For statistical analysis, see the Results. (●, unpunished; ▼, punished.) Reprinted with permission from Heilig et al. 1992.

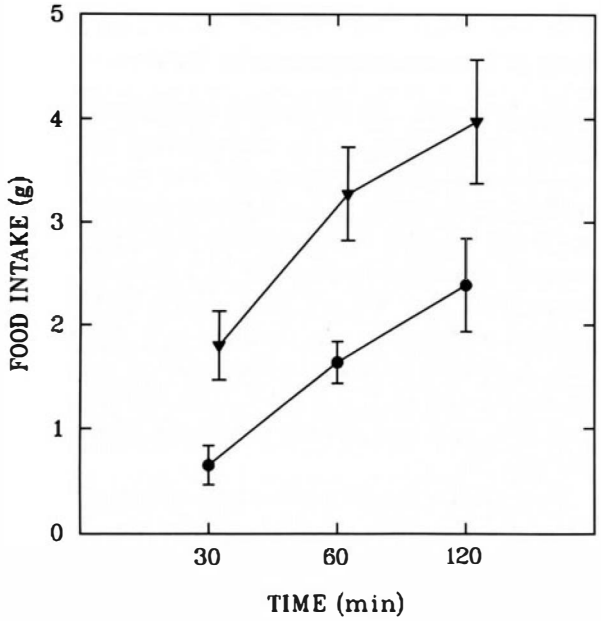


**Figure 2.** Increased food intake after ICV injection of NPY (2.0 nmol) in free-feeding animals. Cumulative food intake during 2 hours is shown (mean ± SEM, $n = 8$). For statistical analysis, see the Results. (●, vehicle; ▼, NPY.)

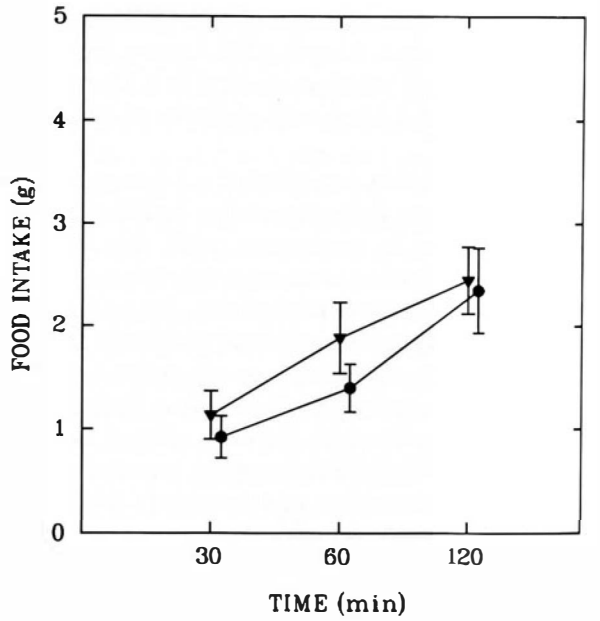


**Figure 3.** Lack of effect on food intake of NPY (100 pmol) injected into the central amygdaloid nucleus. Cumulative food intake during 2 hours is shown (mean ± SEM, $n = 8$). Testing conditions were identical to those in Figure 2. (●, vehicle; ▼, NPY.)

$p < .001$). There was no significant interaction between treatment and time (Fig. 2).

***Pain Threshold.*** In the tail-flick experiment that followed administration of NPY to determine possible effects on pain threshold, no difference in latency to tail flick was seen, indicating that the increase in punished responding was not due to the analgesic effects of NPY (2.5 ± 0.7, 1.7 ± 0.2, and 1.7 ± 0.1 second; mean ± SEM for NaCl, and 0.2, 1.0, and 5.0 nmol NPY, respectively; ($F[26,3] = .77$, $p < .52$, not significant).

## Effects of NPY and Its Analogs in the Central Nucleus of the Amygdala

***Food Intake.*** Free-feeding animals injected with NPY (100 pmol/side) in the central amygdaloid nucleus did not differ from vehicle-treated controls ($F[42,2,2,1] = 1.1$, $p = .32$, not significant; Fig. 3).

***Conflict Behavior After NPY Microinjection.*** Average baseline responding on the unpunished component was 359.6 ± 34.6 lever presses per session, and on the punished component 24.8 ± 0.8 lever presses per session (mean ± SEM). NPY markedly increased punished responding both at the 50 and the 100 pmol/side dose ($F[25,2] = 7.7$, $p = .002$ for overall treatment effect; both groups differed from controls at $p < .01$ on Dunnett's test). Both doses were equally efficacious, indicating an $ED_{50}$ below 50 pmol/side. Unpunished responding was not affected (Fig. 4).

***Conflict Behavior After Microinjections of the Selective NPY-Y1 Receptor Agonist p[Leu$^{31}$,Pro$^{34}$]NPY.*** Average baseline responding on the unpunished component was 307.3 ± 32.5, and on the punished component 22.5 ± 1.6 lever presses per session (mean ± SEM). The Y1 agonist produced an increase of punished responding of a magnitude similar to that seen with native NPY at both 50 and 100 pmol/side ($F[21,2] = 6.7$, $p = .006$ for overall treatment effect; both groups differed from vehicle-injected controls at $p < .01$ on Dunnett's test). Also here, both doses were equally efficacious, indicating an $ED_{50}$ below 50 pmol/side. Unpunished responding was not affected (Fig. 5).

***Conflict Behavior After Microinjection of the Selective NPY-Y2 Agonist NPY$_{13-36}$.*** Average baseline responding on the unpunished component was 319.6 ± 43.6, and on the punished component 25.75 ± 1.8 lever presses per session (mean ± SEM). The Y2 agonist was markedly less potent than NPY in producing a release of punished responding, requiring a dose of 200 pmol/side for a significant effect ($F[23,2] = 4.0$, $p = .033$ for the overall treatment effect; the 100 pmol/side group not significantly different from controls, the 200 pmol/side different at $p = .037$ on Dunnett's test). The unpunished component was not affected (Fig. 6).

## Effects of Intrastriatal Microinjection of NPY

Average baseline responding was 492.9 ± 30.7 on the unpunished, and 17.9 ± 1.5 on the punished compo-

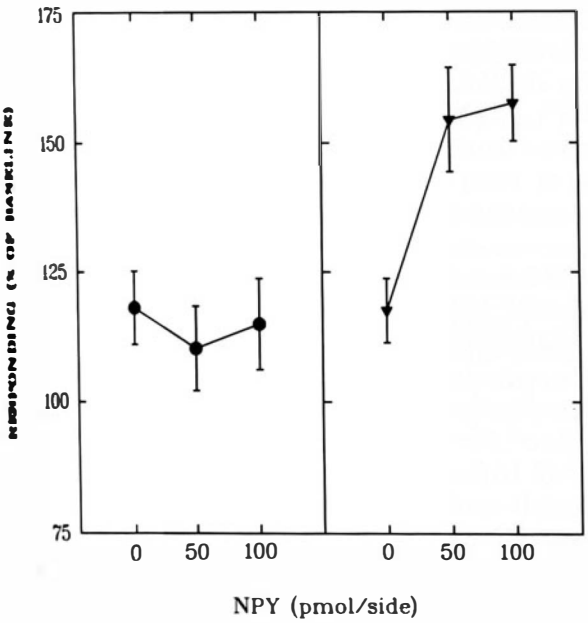


Figure 4. Markedly increased punished (right panel), and unaffected unpunished (left panel) responding in the Geller-Seifter conflict test after injection of NPY (50 to 100 pmol/side) into the central nucleus of the amygdala. Responding is expressed as described in legend to Figure 1. Values are means of 8 to 10 animals, and error bars represent SEM. For statistical analysis, see Results. (●, unpunished; ▼, punished.)

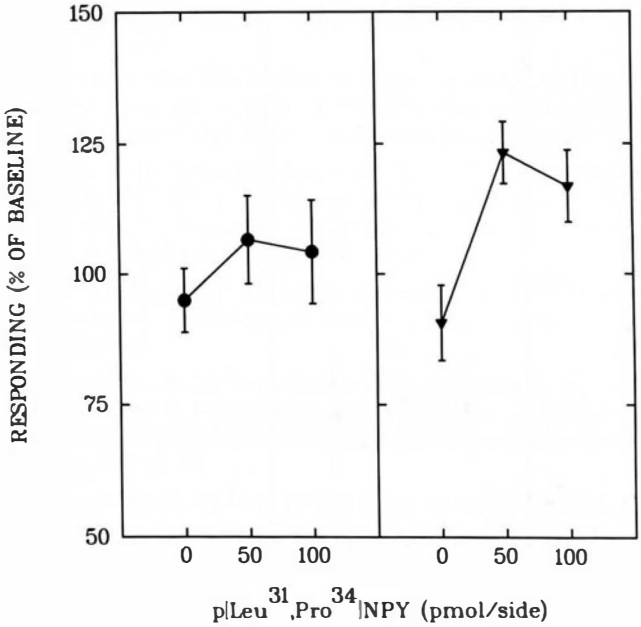


**Figure 5.** Increased punished, and unaffected unpunished responding after injection of the selective NPY-Y1 agonist, p[Leu$^{31}$,Pro$^{34}$]NPY (50 to 100 pmol/side) into the central nucleus of the amygdala. Responding is expressed as described in legend to Figure 1. Values are means of 8 to 10 animals, and error bars represent SEM. For statistical analysis, see Results. (●, unpunished; ▼, punished.)

ment of the conflict test (lever presses per session; mean ± SEM). NPY (100 pmol/side) injected into the nucleus caudatus affected neither unpunished (116.8 ± 16.7% vs. 103.1 ± 14.5% of baseline) nor punished (135.2 ± 14.0% vs. 128.5 ± 15.2% of baseline) responding, showing the site specificity of the effects produced by microinjections into the central nucleus of the amygdala.

## DISCUSSION

In the present study, ICV administration of NPY produced both a robust increase in food intake, and a release of punished responding in the Geller–Seifter conflict test. The latter effect is similar to that seen with prototypical anxiolytics, and is therefore termed "anxiolytic-like." Thus, ICV administration of NPY reproduced previously reported orexigenic and anxiolytic-like effects of the peptide (Clark et al. 1984; Heilig et al. 1989). In the conflict test, however, NPY also produced a smaller increase of unpunished responding, suggesting that increased appetite could contribute to the apparent anxiolytic-like action of NPY in this test.

Anxiolytic-like effects of ICV NPY have previously been reported in the Vogel punished drinking test and in the elevated P-maze (Heilig et al. 1989). These two models do not rely on food reward, and are therefore less sensitive to false-positive results due to effects on food intake mechanisms. It could, however, still be argued that an increased appetitive drive can present a confound in any anxiety model, for example, by stimulating exploration. Recently, an increase of punished milk drinking was reported in mice after ICV administration of NPY (Flood and Morley 1991). Rather than anxiolytic, this effect was interpreted as indicative of "an increased motivation to eat." Thus, other means of separating the orexigenic and anxiolytic-like actions of NPY would be important. Establishing different anatomic substrates for the two effects, and demonstrating the anxiolytic-like action in the absence of increased food intake would support the hypothesis that these two functional effects are independent of each other.

A key brain structure involved in emotionality is the amygdaloid complex. In particular, the amygdaloid complex has been hypothesized to integrate autonomic responses associated with emotion (Smith and DeVito 1984), and it has been proposed that the amygdala codes the stressful affect of aversive inputs. The central nucleus of the amygdala in particular may be the point of output to areas controlling visceral responses to such information (Henke 1988). The central nucleus receives a dense network of NPY-ergic terminals (Chronwall et al. 1985), which innervate neurons projecting to the dorsal vagal complex (Gray et al. 1986). Neuropeptide Y-positive terminals in the central nucleus originate at least in part from cell bodies in the nucleus of the soli-

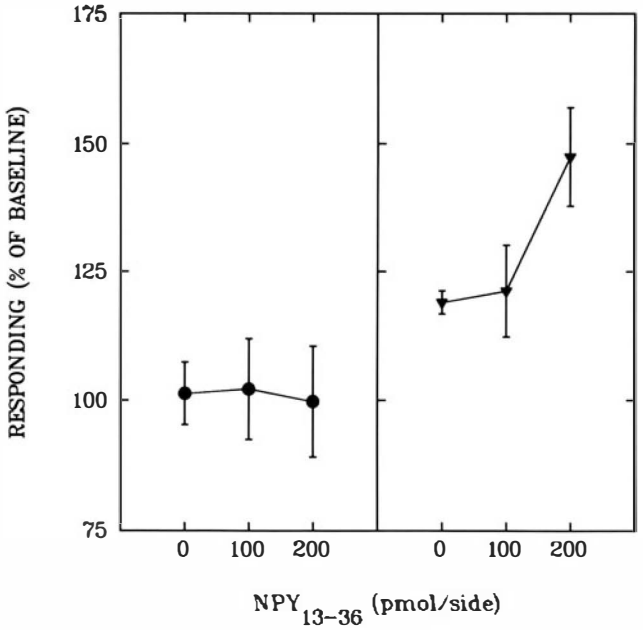


**Figure 6.** Unpunished and punished responding after injection of vehicle, or the selective NPY-Y2 agonist, $NPY_{13-36}$ (100 to 200 pmol/side) into the central nucleus of the amygdala. The figure illustrates the lower potency of the Y2 agonist, which required a dose of 200 pmol/side to produce a marginally significant increase of punished responding. Responding is expressed as described in legend to Figure 1. Values are means of 8 to 10 animals, and error bars represent SEM. For statistical analysis, see Results. (●, unpunished; ▼, punished.)

tary tract. In a vast majority (80%) of these afferents, NPY is colocalized with norepinephrine (Zardetto-Smith and Gray 1990, Riche et al. 1990).

In the present study, doses of NPY as low as 50 pmol/side injected into the amygdala produced a maximal anxiolytic-like effect in the conflict test. No effects on the nonspecific, unpunished component of the test were seen. In a separate experiment, a higher NPY dose (100 pmol/side) did not increase food intake in free-feeding rats after microinjection into the central nucleus. These observations are in agreement with studies by others. It has previously been shown that doses in this range increase food intake after injection into the hypothalamic paraventricular nucleus (Stanley and Leibovitz 1985), but are without effect on this parameter after administration into the amygdala (Stanley et al. 1985). The results of the present study support the hypothesis that the anxiolytic-like action of NPY is independent of the peptide's orexigenic effects, that the two effects are mediated by different anatomic structures, and that the central amygdaloid nucleus, at least in part, mediates the anxiolytic-like effects of NPY.

A heterogeneity of NPY receptors was initially proposed in the peripheral nervous system. It was suggested that one receptor population, termed Y1, required the full amino acid sequence of NPY for activation, although Y2 receptors could also be activated by shorter, C-terminal fragments of NPY, such as $NPY_{13-36}$ (Wahlestedt et al. 1986). Evidence from functional studies as well as binding experiments (Heilig et al. 1988; Wahlestedt et al. 1990; Aicher et al. 1991) confirmed that a similar heterogeneity of NPY receptors was also present in the brain. In a previous study, ICV administration of NPY produced anxiolytic-like effects, and $NPY_{13-36}$ was ineffective. Based on this negative evidence, it was hypothesized that anxiolytic-like actions of NPY are likely to be mediated by Y1 receptors (Heilig et al. 1989). Recently, a selective Y1 agonist, p[$Leu^{31}$,$Pro^{34}$]NPY became available (Fuhlendorff et al. 1990). In the present study, the Y1 agonist was approximately equipotent with native NPY in producing a release of punished responding, and $NPY_{13-36}$ was markedly less potent. Such a hierarchy of potencies is characteristic of the recently cloned Y1 receptor (Larhammar et al. 1992). These results therefore represent the first positive evidence that the anxiolytic-like action of NPY is mediated by Y1 receptors. In peripheral sympathetic neuroeffector junctions, NPY coexists with norepinephrine, and potentiates postsynaptic actions of the latter transmitter by activating Y1 receptors (Wahlestedt et al. 1990). Since a similar colocalization seems to be present in the central amygdaloid nucleus (Zardetto-Smith and Gray 1990; Riche et al. 1990), NPY could exert its anxiolytic-like effect on this structure in an analogous manner. However, NPY in the amygdala also coexists with somatostatin and gamma-aminobutyric acid in a population of intrinsic interneurons similar to those seen in the neocortex and striatum (McDonald 1989; McDonald and Pearson 1989). It remains to be established whether brain-stem afferents, local interneurons, or both are involved in mediating the anxiolytic-like effects of NPY.

It has been reported that the concentration of NPY-like immunoreactivity is decreased in the cerebrospinal fluid of depressed patients (Widerlöv et al. 1988) and in brain tissue of suicide victims (Widdowson et al. 1992), suggesting that NPY could be involved in the pathogenesis of the depressive syndrome, or parts thereof. Interestingly, in the depressed patient population, a negative correlation between NPY-like immunoreactivity and anxiety scores was observed. Furthermore, high-performance liquid chromatography analysis of the immunoreactive material revealed that only a single peak, coeluting with native NPY was present in the controls, whereas peaks representing immunoreactive material of smaller molecular size were also detected in the patients (Heilig and Widerlöv 1990). The results of the present study suggest that activation of Y1 receptors is required to produce antianxiety effects of NPY. Such an activation would require the full sequence of NPY. An increased processing and/or me-

metabolism of NPY to shorter fragments could therefore eliminate an important endogenous antianxiety signal, and thus might contribute to anxiety symptoms seen in depression.

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