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PCP alters regional concentrations of neuropeptide Y and peptide YY in rat brain

**Kazuo Sakai, Kiyoshi Maeda, Shigeru Okuyama
and Chikako Tanaka**

From the Department of Psychiatry, Kobe University School of Medicine (KS), Kobe 650 Japan, Hyogo Institute for Aging Brain and Cognitive Disorders(KS, KM, CT), Himeji 670 Japan, and Medical Research Laboratories, Taisho Pharmaceutical Co., LTD. (SO), Ohmiya 330 Japan

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Address reprint requests to Kiyoshi Maeda, MD, Hyogo Institute for Aging Brain and Cognitive Disorders, 520 Saisho-koh, Himeji 670 Japan, phone 81-792-95-5511, fax. 81-792-95-8199.

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The psychotomimetic effects of PCP often have a delayed onset and extend far from the time plasma drug levels reach their peak. PCP at a low dose is considered selective for actions on the NMDA-PCP receptor. We evaluated effects of PCP (2 and 10 mg/kg, i.p.) on regional content of neuropeptide Y (NPY)-like immunoreactivity (LI) and peptide YY (PYY)-LI, in the rat brain. Thirty min after administration of PCP, NPY-LI levels were significantly elevated in some limbic structures following both doses. A significant, widespread increase in NPY-LI levels was induced 2 hrs after administration of the higher dose of PCP. On the contrary, NPY-LI was significantly decreased in a number of the regions 24 hrs after PCP. The extent of reduction was less following the higher dose of PCP than the lower dose. PCP did not cause a consistent effect on PYY-LI. The findings suggest that effects of PCP on brain NPY content might depend on the dose and the interval between administration of the drug and sacrifice.

Introduction

Phencyclidine (1-[1-phenylcyclohexyl]piperidine, PCP) is a psychotomimetic agent, which induces not only productive (positive), but deficit (negative) schizophrenic symptoms in man (Javitt and Zukin 1991). The cognitive and neuropsychological deficits in PCP psychosis are highly similar to those of schizophrenia (Davies and Beech 1960, Bakker and Amini 1961). PCP has been regarded as a tool for research of schizophrenia, similar to amphetamines and lysergic acid diethylamide (LSD) (Rosenbaum et al 1959). While PCP, at moderate and high dose ranges, has actions on a number of neurotransmitter receptors, PCP acts selectively on its own receptors, PCP binding sites of the N-methyl-D-aspartate (NMDA)-type excitatory amino acid receptor complex, at low doses (Javitt and Zukin 1991). Furthermore, the psychotomimetic effects of the drug are often delayed in onset and prolonged in duration (Aniline and Pitt 1982). Recently, lower doses of PCP have been proved to decrease cerebral glucose metabolism 24 hrs after the drug administration, which is not consistent with drug kinetics (Gao et al 1993).

Neuropeptide Y (NPY), a 36-amino-acid peptide initially isolated from the porcine brain, is one of the most widely distributed peptides in the brain. NPY is a member of the pancreatic polypeptide (PP) family along with peptide YY (PYY) and PP (Tatemoto et al 1982). When administered into the CNS of experimental animals, NPY produces sedation (Heilig et al 1988), enhances memory retention (Flood et al 1987), and stimulates excessive intake of food and water (Stanley and Leibowitz 1984). PYY has been identified as the third member of the PP family by Tatemoto et al (1982). Although PYY was first isolated from porcine intestine and subsequently found in the CNS, the functional role of the peptide still remains to be investigated. The alteration in the metabolism of these peptide in patients with schizophrenia has been postulated (Heilig and Widerlöv 1990). Elevation in NPY (Peters et al 1990) and reduction in PYY concentrations have been reported in the cerebrospinal fluid (CSF) of drug-free chronic schizophrenic patients (Widerlöv et al 1988), while no differences were also reported in CSF NPY between patients with schizophrenia and normal

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volunteers (Berrettini et al 1987, Widerlöv et al 1988). Frederiksen et al (1991) have shown that both peptide concentrations are reduced in the temporal cortex of schizophrenic patients.

In the present experiments we examined the dose characteristics and time course of the PCP action on the concentrations of NPY and PYY in 14 brain regions in the rat.

Materials and methods

Male Wistar rats (250-300g) were maintained in a light- and temperature-controlled room ($23 \pm 1^\circ\text{C}$, a 12 hr-light cycle starting at 7:00 am).

Administration of phencyclidine

PCP-HCl (synthesized by Taisho Pharmaceutical Co. Ltd., Tokyo, Japan, Ogawa et al 1994) was dissolved with 0.9% saline. The solution was intraperitoneally injected with a volume of 1 ml/kg at doses of 2 or 10 mg/kg. The control rats received the corresponding volume of saline. The rats were sacrificed by decapitation at various intervals (30 min, 2 hrs and 24 hrs) after the i.p. injection.

Dissection of the brain and extraction of peptides

The brains were immediately removed and stored at -80°C . Then the brains were sliced into 2 mm thickness and dissected according to a modification (Kaneda and Maeda 1994) of the method originally reported by Palkovits and Brownstein (1988). The brain was dissected into 14 regions; the medial prefrontal cortex (mPFC), lateral prefrontal cortex (lPFC), motor area of frontal cortex (FC), temporal cortex (TC), parietal cortex (PC), occipital cortex (OC), anterior cingulate cortex (aCg), posterior cingulate cortex (pCg), hippocampus (Hp), amygdala (Am), accumbens nucleus (Acb), septum (Sp), the hypothalamus (Ht) and striatum (St). In the present experiment the limbic areas were referred to aCg, pCg, Hp, Am, Acb and Sp, and the cortical regions designated mPFC, lPFC, FC, TC, PC and OC.

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Tissue containing peptides were extracted using the method of Maeda et al. (1993); each sample was homogenized by ultrasonication in ice cold 2 N acetic acid. After measuring the protein concentrations by the method of Lowry et al (1951), the homogenate was placed in boiling water for 5 min to inactivate degrading enzymes and then centrifuged. The supernatant was lyophilized and reconstituted with an assay buffer containing 0.05 M sodium phosphate, 0.08 M NaCl, 0.025 M EDTA, 0.02% sodium azide and 1% bovine serum albumin.

Radioimmunoassays (RIAs) of peptides

NPY was measured by a specific RIA, as reported previously (Kakigi and Maeda 1992). [125 I]-Bolton Hunter labeled Lys⁴ porcine NPY was purchased from New England Nuclear Japan (NEX-222, Tokyo, Japan). The specific activity was 2200 Ci/mmol (486 mCi/ mg). The anti-NPY serum was raised in New Zealand White rabbits. The detailed characterization of the antiserum was reported elsewhere (Maeda et al., 1994). The antiserum did not cross-react to the related peptides, rat and human PP and PYY, at up to 1 mg/0.1 ml. The dilution of the antiserum was $1:4 \times 10^4$. Synthetic NPY (Bachem Fine Chemicals, Switzerland) was used as the standards. The least detectable amount of NPY was 0.4 pg/tube.

For determination of PYY a commercially available antiserum (Rabbit anti-porcine PYY serum, RAS 7173, Lot No. 019353, Peninsula Laboratories Inc.) and [125 I]iodotyrosyl PYY (Y-7173, Amersham Japan) were purchased. The specific activities of the [125 I]PYY were 995-1520.2 Ci/mmol. and the dilution of the antiserum was $1:3 \times 10^5$ dissolved in 0.1% Triton X-100. According to the data sheet provided by Peninsula laboratories, the cross-reactivities to NPY and PP of this antiserum were 0.012% and 0.002%, respectively. No cross-reactivities were observed to vasoactive intestinal peptide, avian PP, substance P and Met-enkephalin. Synthetic PYY was used as the standards (Bachem Fine Chemicals, Switzerland). Separation of bound [125 I]PYY from free was performed using Pansorbin (Sigma Chemical, U.S.A.). The IC₅₀ was 5-18.5 pg/ tube. The least detectable amount was less than 2

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pg/tube. The rest of the assay procedure was the same as that of NPY. The displacement curve generated by rat brain extracts was parallel to that by synthetic porcine PYY.

The peptide-LI was determined in duplicates. The control and the experimental samples at each time interval were run in a single assay to eliminate intra-assay variations.

Statistical analysis

Data were analyzed using one-factor ANOVA. If the F ratio was significant, the non-paired Student's t test was used to compare differences between the means of individual groups.

Results

Alterations in NPY-LI 30 min and 2 hrs after PCP

Changes in NPY-LI 30 min after the administration of PCP are shown in Figure 1. Significantly elevated levels of the peptide-LI were found in two limbic regions, aCg and Acb. A dose-related increase was found in Acb. There were no changes in NPY levels in the other regions. A highly significant increase in NPY-LI was seen 2 hrs after the administration of 10 mg/kg of PCP throughout the brain (Figure 2). A significant increase was observed in 8 of 14 regions (144% in TC to 188% in Ht). After the higher dose of the compound NPY-LI was elevated in 4 of 6 neocortical regions and 3 of 6 limbic areas. The lower dose of PCP induced a significant elevation of NPY-LI in FC, Hp and Acb. On the contrary, significant decreases were found in two limbic structures, the Am and Sp following the lower dose of PCP. Interestingly, a dose-dependent decrease was seen in the St.

Alterations in NPY-LI 24 hrs after PCP

No increases in NPY-LI were obtained in any regions by either dose of PCP at 24 hrs.

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We found a significant reduction after administration of 2 mg/kg PCP in 2 out of 6 neocortical regions, FC (53.1%) and OC (47.2%), and in 5 out of 6 limbic structures, aCg (53.8%), pCg (57.1%), Hp (51.3%), Sp (46.7%) and Acb (67.7%). Thus, the reduction of NPY-LI by 2 mg/kg of PCP was predominantly observed in the limbic structures. Reduced levels of NPY-LI were also found in mPFC, OC and aCg in the rats receiving 10 mg/kg of PCP. The higher dose of PCP appeared to be less potent to reduce NPY-LI levels, compared to the lower dose. Administration of the compound resulted in a dose-related decrease in striatal NPY-LI after 24 hours (Figure 3), similar to the results at 2 hrs.

Alterations in PYY-LI following PCP

PYY-LI did not change 30 min after injection of either 2 or 10 mg/kg PCP except in the OC, where a reduction was observed in the rats treated with 10 mg/kg of PCP (Figure 4). Two hours after injection, an increase in LPFC and a reduction in Ht were found in PYY-LI levels, and both were dose-dependent. Another increase was observed in TC of the rats received 10 mg/kg PCP (Figure 5). The elevation in PYY-LI was shown only in mPFC and FC 24 hrs after the higher dose of PCP, whereas the decrease of PYY-LI was observed in Hp of the rats treated with 10 mg/kg PCP and in Ht of the rats treated with both 2 and 10 mg/kg PCP (Figure 6).

4. Discussion

A better understanding of the molecular mechanism of action of PCP is especially important, since PCP-induced psychosis resembles schizophrenia (Quirion et al 1984). The presence of a highly specific and selective binding site for PCP strongly suggests the existence of endogenous ligands for these binding sites. It is of great value to isolate putative endogenous ligands for PCP binding site. Recent studies have shown that NPY and PYY have strong affinities for PCP binding sites (Roman et al 1989), although contradictory results have been reported (Tam and Mitchell 1991). If these peptides are endogenous ligands for PCP binding sites

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(Monnet et al 1992, Bouchard et al 1993), alteration in the peptide content following treatment with PCP is expected in the brain.

NPY-LI changes 30 min and 2 hours after PCP

PCP is known to exhibit various dose-dependent actions in experimental animals. The actions on NPY-LI levels also seem to be dose-specific. In the present study, we found that PCP, at both 2 and 10 mg/kg, increased NPY-LI content at 30 min and that the increase was restricted to two limbic regions. It is of interest that the changes in NPY-LI induced by PCP occur first in these structures, since both structures are reported to modulate the interaction between the neocortex and limbic structures (Csernansky et al 1991). The marked, widespread elevation in NPY-LI 2 hrs after 10 mg/kg of PCP has not been demonstrated before, since no previous studies evaluated the changes in NPY-LI within 6 hrs after the administration of PCP (Midgley et al 1992, Midgley et al 1993). This rise was observed in both cortical and limbic regions to a similar extent. PCP has been shown to produce an initial increase in glucose metabolism at 3 hrs after a higher dose (8.6 mg/kg), which is not seen after a lower dose (0.86 mg/kg) (Gao, et al 1993).

NPY-LI changes 24 hours after PCP

On the other hand, PCP caused a decrease in NPY-LI levels after 24 hrs. Ten mg/kg of PCP was less potent in reducing NPY-LI levels than 2 mg/kg. Midgley et al (1993) observed the reduction of NPY-LI in the nucleus accumbens at 6 hrs and in the frontal cortex at 12 hrs by the administration of 15 mg/kg of PCP. These data would imply that a large dose of PCP elevated NPY-LI throughout the brain shortly after the administration. It is also suggested that PCP at a low dose, had a delayed effect resulting in reducing NPY-LI levels in the rat brain. The lower dose of PCP decreased NPY-LI in limbic areas, the amygdala and septum, at 2 hrs in spite of no effects or non-significant increases in the neocortical areas. The reduction of NPY-LI was found in all limbic areas except the amygdala and in only 2 out of 6 cortical

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regions 24 hrs following 2 mg/kg PCP. The lowering effect of low dose PCP in NPY-LI levels appears to be predominantly in the limbic system rather than cortical areas. Gao et al (1993) have reported that PCP-induced alterations in glucose metabolism are most prominent in the limbic system and can be detected at low doses. The limbic system is suspected to be functionally involved in both PCP psychosis and schizophrenia (Tamminga et al 1987, Csernansky et al 1991, Tamminga et al 1992). It is known that the action of low doses of PCP is rather specific, while PCP interacts with a large number of target sites at high doses (Raja and Guyenet 1980, Tanii et al 1990, Javitt and Zukin 1991). These data may suggest that NPY has a role in the specific effect of low doses of PCP in the limbic system.

Biphasic changes in NPY-LI following PCP

NPY-LI in the frontal cortex, hippocampus and nucleus accumbens following 2 mg/kg of PCP and the occipital cortex and anterior cingulate cortex following 10 mg/kg of PCP showed a biphasic change in our present study. An injection of PCP produced an initial increase in NPY-LI levels at 2 hrs and a later decrease at 24 hrs in these regions. The tissue content of peptides is the consequence of alteration in both release and synthesis of peptides. An initial increase in NPY-LI levels at 2 hrs, *e.g.*, may be due to either increased synthesis or reduced release of the peptide. The fact, however, that acute administration of PCP produced a rapid increase in NPY-LI content in certain regions as soon as 30 minutes after administration suggests that the initial effect may be attributed to reduced release, although the possibility of increased synthesis cannot be ruled out.

A similar biphasic change of PCP action has been shown in cerebral glucose metabolism. Gao et al (1993) have reported a biphasic action of PCP, an increase followed by a decrease in limbic areas and limbic-associated structures. The authors have suggested the association of this delayed cerebral hypometabolism with the psychotomimetic effects of PCP. The change of NPY-LI by PCP parallels this metabolic change. Ogawa et al (1994) have proposed that an animal receiving lower

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doses (1.0-2.0 mg/kg) of PCP is a useful model of schizophrenia, since this animal model shows cognitive dysfunctions without stereotyped behavior or hyperlocomotion induced by higher doses of PCP (5-10 mg/kg). Considering these findings, the effect of the low dose of PCP seems to be related to the deficit schizophrenic syndrome induced by PCP.

Mechanism by which PCP alters NPY-LI levels

The mechanism by which PCP modulates NPY-LI levels in the brain is not known at present. NPY content in the brain is regulated by a number of neurotransmitter systems. Midgley et al (1992) have evaluated the role of neurotransmitter systems in PCP-induced reductions of striatal NPY and have found that the effect of the non-competitive NMDA receptor antagonist, MK-801, on striatal NPY content resembles that of PCP. They have suggested that the NPY system is regulated by NMDA receptor function. They have also observed that dopamine D1 antagonists significantly attenuate PCP-induced changes. We found, in the present experiment, a dose-related decrease in striatal NPY-LI levels both 2 and 24 hrs after injections of PCP. We have demonstrated the roles in NPY metabolism of serotonergic systems (Kakigi and Maeda 1992), dopaminergic systems (Maeda et al 1993), and NMDA receptor functions (Kaneda and Maeda 1994). We (Maeda et al 1993) and another group (Engber et al 1992) have found that the regulation of striatal NPY by the dopaminergic system is different from that in other regions, *e.g.*, the cerebral cortex. The influence of PCP on striatal NPY regulation appears to be similar to that of dopaminergic agonists. PCP inhibits dopamine uptake *in vitro* and increases firing rate of dopaminergic neurons in the substantia nigra (Raja and Guyenet 1980). Therefore, PCP may affect NPY metabolism through the dopaminergic system.

PCP has an affinity for the sigma receptor to which psychotomimetic benzomorphanes and some antipsychotic drugs preferentially bind (Zukin et al 1984). Recent studies have shown that NPY and PYY have strong affinities for the rat brain sigma binding sites (Roman et al 1989). It has been suggested that these peptides

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have a modulatory role at the NMDA receptor complex through an interaction with the sigma receptor (Roman et al 1991). NPY and PYY have been indicated to be involved in ion transport in mouse jejunum through sigma sites (Riviere et al 1993). We have demonstrated that chronic administration of haloperidol, which is effective against PCP psychosis and is reported to act on sigma receptors, results in a widespread increase of NPY-LI in the rat brain (Sakai et al 1995). Therefore, PCP may act on sigma receptors resulting in a decrease of NPY-LI. This effect of haloperidol, however, may be ascribed to its action on D2 receptors, since haloperidol is a potent D2 receptor blocker. NPY has been described to interact with the γ -aminobutyric acid (GABA) system in the rat (Massari et al 1988). Midgley et al (1992) have found an inhibition by GABA agonists of PCP-induced reduction in striatal NPY-LI levels. Furthermore, they have observed that treatment with MK-801 decreases striatal NPY content, and that this effect is blocked by GABA agonists. They have suggested the mediation by GABAergic systems of the glutamatergic modulation of the striatal NPY neurons. Our results of a reduction in NPY-LI levels after PCP administration 24 hrs after PCP administration might be consequence of the altered function in the GABAergic system by PCP.

Ekman et al (1986) determined the concentration of PYY-LI in rat brain for the first time. They reported one tenth to one fifth concentration of PYY-LI in the hypothalamus, compared to our data. They did not detect PYY-LI in the cortex, striatum, septum and nucleus accumbens. The differences between these two studies remain unknown. Frederiksen et al (1991) have reported a similar concentration of PYY-LI to ours in the cortex and hypothalamus of the human brain. Reduced PYY levels in the temporal cortex (Frederiksen et al 1991) and CSF (Widerlöv et al 1988) of schizophrenic patients have been described, while functional roles of this alteration still remain obscure. The present study demonstrated no consistent alterations by PCP in PYY-LI levels in any region except the hypothalamus, where PYY-LI decreased 2 hrs and 24 hrs after the administration of both doses of PCP. The significance of effects of PCP on PYY in the hypothalamus remains to be

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investigated.

In summary, a large dose of PCP resulted in an increase of NPY-LI in the brain shortly after the administration and a low dose of PCP caused a delayed decrease at 24 hours. This delayed action of a low dose of PCP on brain NPY may be relevant to PCP psychosis.

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Figure Legends

Figure 1. Effects of phencyclidine (PCP), 2 mg/kg and 10 mg/kg, on regional brain levels of neuropeptide Y-like immunoreactivity (NPY-LI) in the rat. Animals (six per group) received PCP intraperitoneally 30 min before sacrifice. The values are % of the means of the controls. The vertical bars are mean \pm S.E.M. Abbreviations used are shown in the Materials and methods section. The NPY-LI (pg/mg protein) in the control rats were as follows: 132.07 \pm 22.66 in mPFC, 111.12 \pm 12.86 in IPFC, 133.61 \pm 9.70 in FC, 120.25 \pm 11.72 in TC, 106.29 \pm 8.40 in PC, 93.20 \pm 6.46 in OC, 105.09 \pm 7.93 in aCg, 84.06 \pm 9.66 in pCg, 66.55 \pm 9.63 in Hp, 192.21 \pm 11.50 in Am, 154.46 \pm 12.86 in Acb, 71.96 \pm 9.32 in Sp, 77.14 \pm 5.08 in St, and 529.88 \pm 60.42 in Ht.

Figure 2. Effects of phencyclidine (PCP), 2 mg/kg and 10 mg/kg, on regional brain levels of neuropeptide Y-like immunoreactivity (NPY-LI) in the rat. Animals (six per group) received PCP intraperitoneally 2 hrs before sacrifice. The values are % of the means of the controls. The vertical bars are mean \pm S.E.M. Abbreviations used are shown in the Materials and methods section. The NPY-LI (pg/mg protein) in the control rats were as follows: 61.97 \pm 4.95 in mPFC, 55.56 \pm 2.83 in IPFC, 46.84 \pm 2.38 in FC, 62.86 \pm 7.27 in TC, 63.97 \pm 6.35 in PC, 68.32 \pm 4.81 in OC, 67.27 \pm 5.28 in aCg, 55.27 \pm 5.13 in pCg, 93.16 \pm 5.88 in Hp, 133.99 \pm 6.86 in Am, 68.25 \pm 4.49 in Acb, 83.57 \pm 15.60 in Sp, 166.75 \pm 8.21 in St, and 262.56 \pm 13.11 in Ht.

Figure 3. Effects of phencyclidine (PCP), 2 mg/kg and 10 mg/kg, on regional brain levels of neuropeptide Y-like immunoreactivity (NPY-LI) in the rat. Animals (six per group) received PCP intraperitoneally 24 hrs before sacrifice. The values are % of the means of the controls. The vertical bars are mean \pm S.E.M. Abbreviations used are shown in the Materials and methods section. The NPY-LI (pg/mg protein) in the control rats were as follows: 380.89 \pm 67.43 in mPFC, 151.01 \pm 6.06 in IPFC, 132.92 \pm 18.77 in FC, 83.04 \pm 11.44 in TC, 101.86 \pm 7.27 in PC, 103.03 \pm 10.18 in OC, 160.60 \pm 7.06 in aCg, 107.70 \pm 12.08 in pCg, 178.43 \pm 17.22 in

Hp, 157.53 ± 10.63 in Am, 270.13 ± 4.94 in Acb, 57.61 ± 5.21 in Sp, 248.02 ± 29.68 in St, and 624.93 ± 29.79 in Ht.

Figure 4. Effects of phencyclidine (PCP), 2 mg/kg and 10 mg/kg, on regional brain levels of peptide YY-like immunoreactivity (PYY-LI) in the rat. Animals (six per group) received PCP intraperitoneally 30 min before sacrifice. The values are % of the means of the controls. The vertical bars are mean \pm S.E.M. Abbreviations used are shown in the Materials and methods section. The PYY-LI (pg/mg protein) in the control rats were as follows: 13.98 ± 0.99 in mPFC, 13.52 ± 1.20 in IPFC, 8.31 ± 0.16 in FC, 9.54 ± 0.43 in TC, 8.47 ± 0.15 in PC, 13.93 ± 0.16 in OC, 12.86 ± 0.30 in aCg, 15.70 ± 0.42 in pCg, 5.36 ± 0.08 in Hp, 5.05 ± 0.17 in Am, 4.04 ± 0.09 in Acb, 3.10 ± 0.10 in Sp, 4.09 ± 0.11 in St, and 4.29 ± 0.07 in Ht.

Figure 5. Effects of phencyclidine (PCP), 2 mg/kg and 10 mg/kg, on regional brain levels of peptide YY-like immunoreactivity (PYY-LI) in the rat. Animals (six per group) received intraperitoneally PCP 2 hrs before sacrifice. The values are % of the means of the controls. The vertical bars are mean \pm S.E.M. Abbreviations used are shown in the Materials and methods section. The PYY-LI (pg/mg protein) in the control rats were as follows: 16.19 ± 1.16 in mPFC, 15.27 ± 0.63 in IPFC, 9.83 ± 0.49 in FC, 10.88 ± 0.24 in TC, 12.76 ± 0.44 in PC, 9.09 ± 0.25 in OC, 17.94 ± 0.87 in aCg, 10.79 ± 0.72 in pCg, 5.85 ± 0.69 in Hp, 5.43 ± 0.38 in Am, 2.43 ± 0.24 in Acb, 3.16 ± 0.42 in Sp, 7.48 ± 0.801 in St, and 11.38 ± 1.94 in Ht.

Figure 6. Effects of phencyclidine (PCP), 2 mg/kg and 10 mg/kg, on regional brain levels of peptide YY-like immunoreactivity (PYY-LI) in the rat. Animals (six per group) received PCP intraperitoneally 24 hrs before sacrifice. The values are % of the means of the controls. The vertical bars are mean \pm S.E.M. Abbreviations used are shown in the Materials and methods section. The PYY-LI (pg/mg protein) in the control rats were as follows: 9.75 ± 0.46 in mPFC, 10.40 ± 0.94 in IPFC, 3.70 ± 0.66 in FC, 22.26 ± 2.29 in TC, 6.88 ± 0.76 in PC, 5.68 ± 0.51 in OC, 12.26 ± 1.42 in aCg, 4.96 ± 0.47 in pCg, 18.27 ± 1.31 in Hp, 16.95 ± 1.84 in Am, 11.91 ± 0.96 in Acb, 14.22 ± 1.89 in Sp, 12.15 ± 1.31 in St, and 15.39 ± 0.75 in Ht.

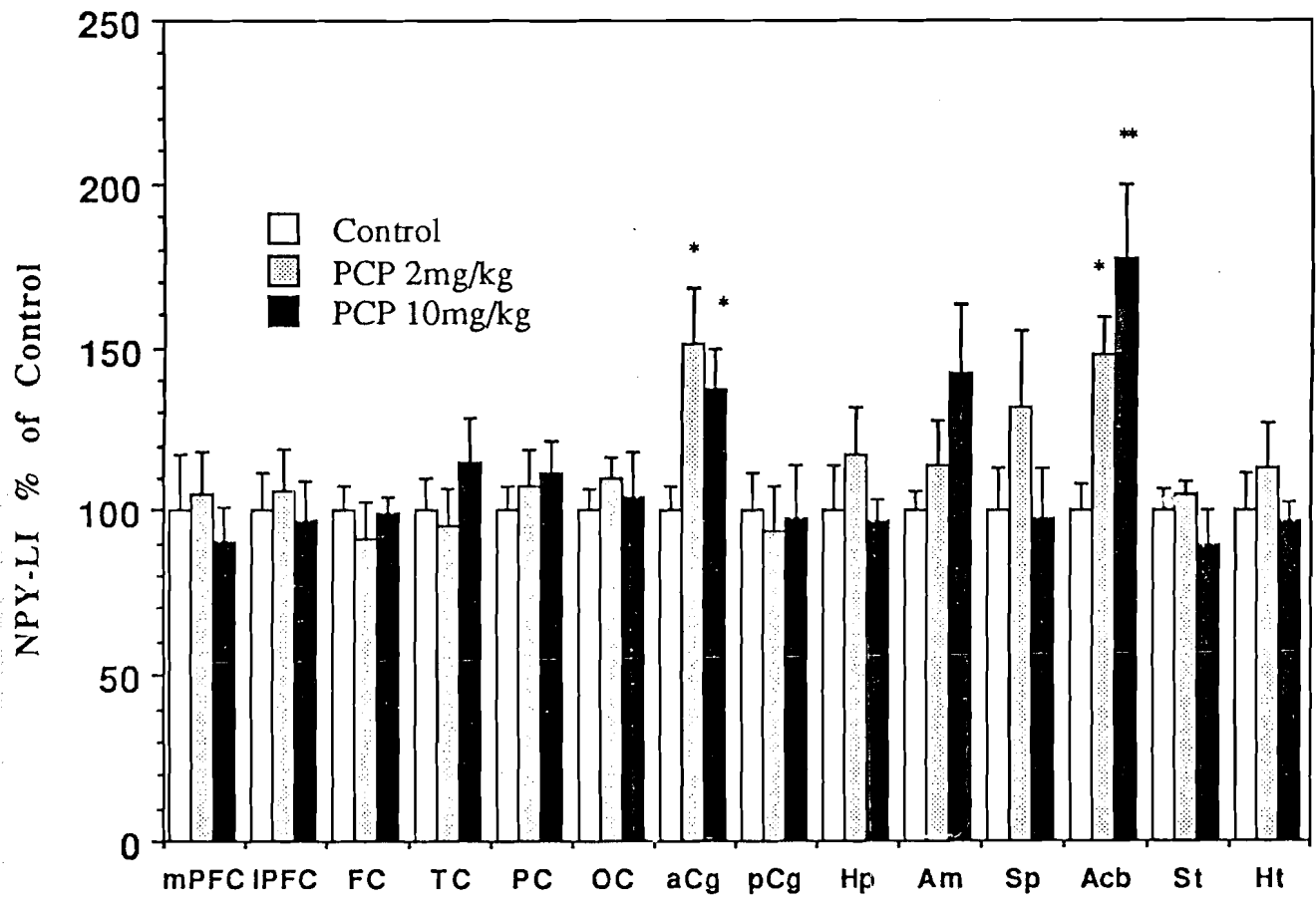


Fig 1

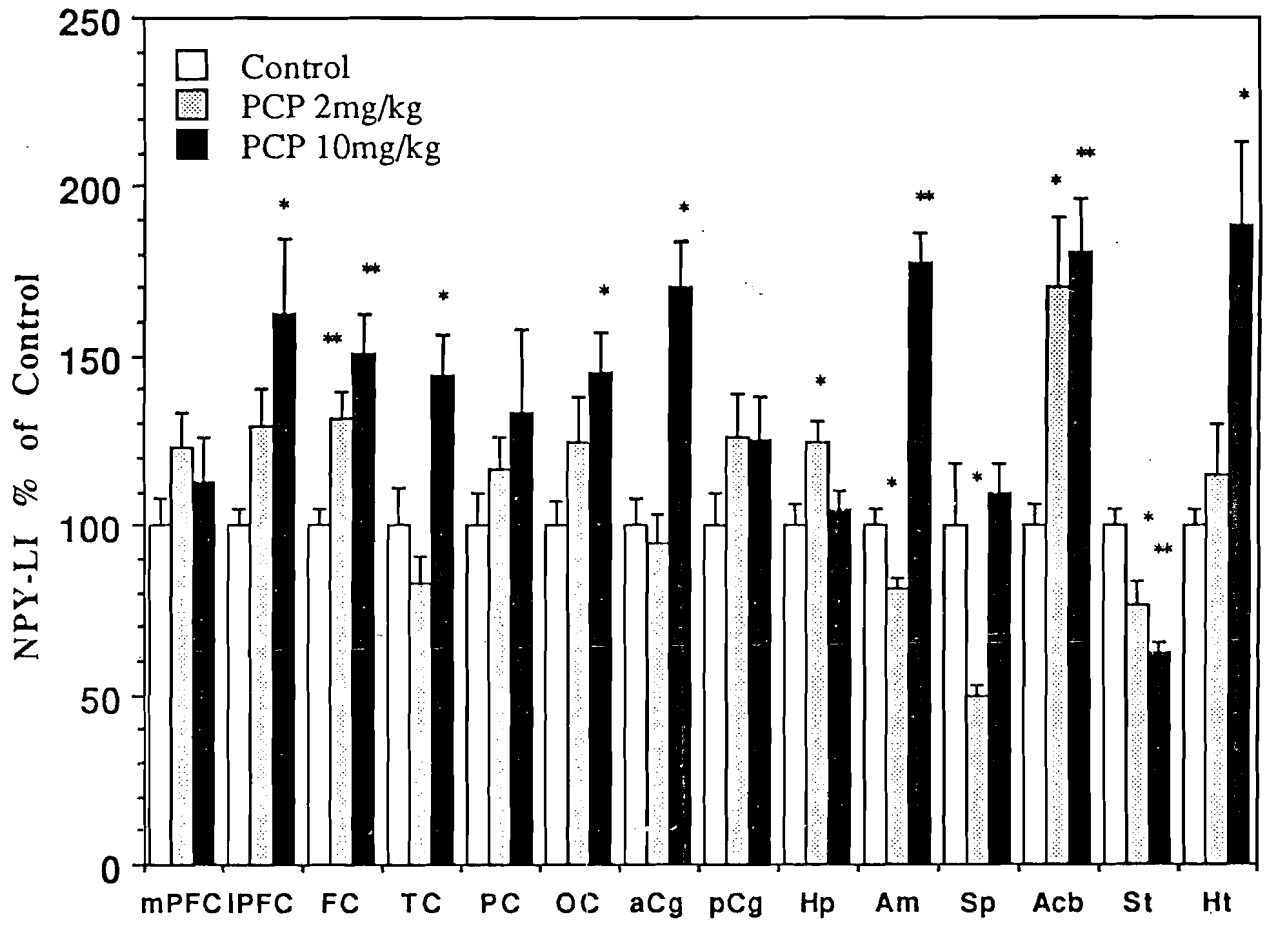


Fig 2

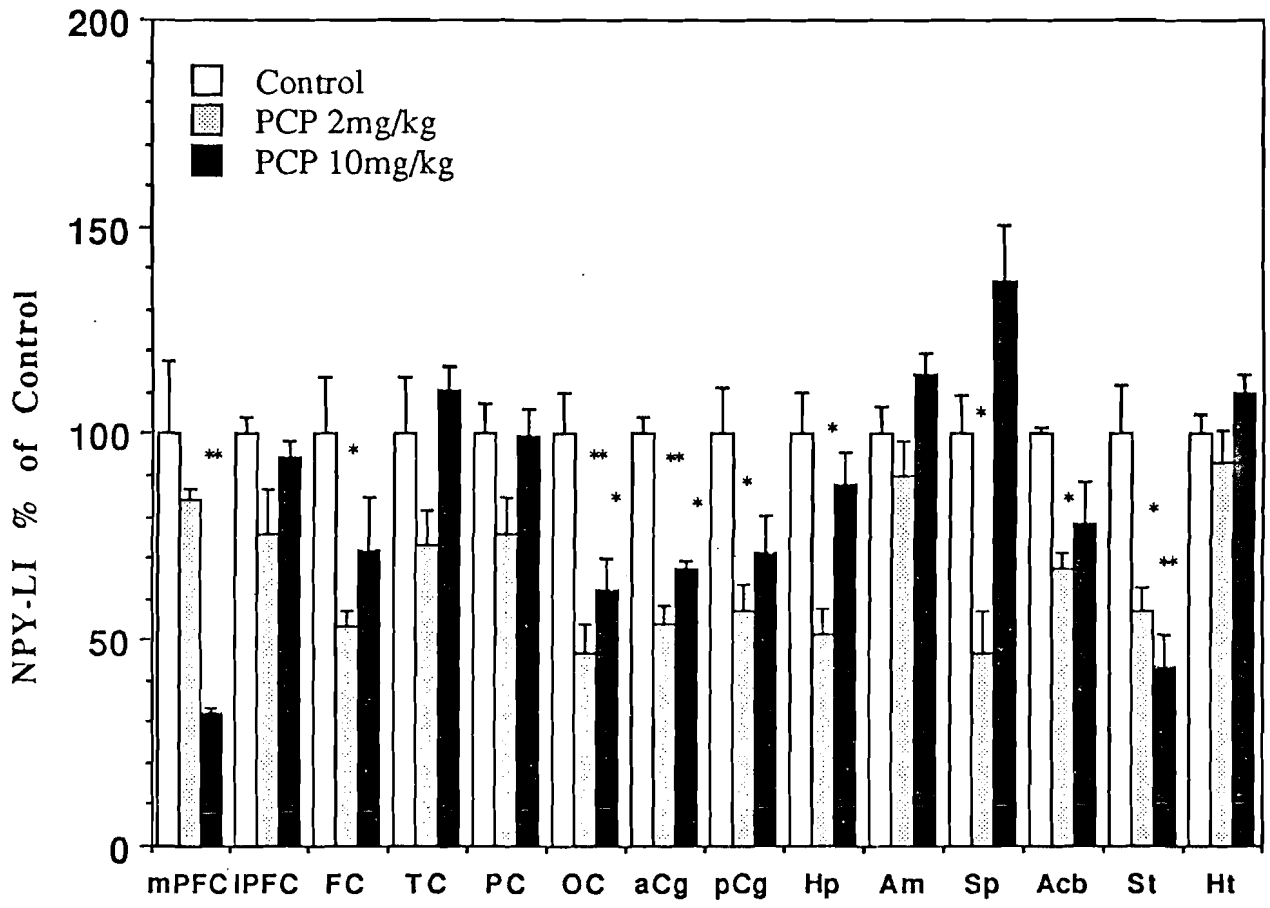


Fig 3

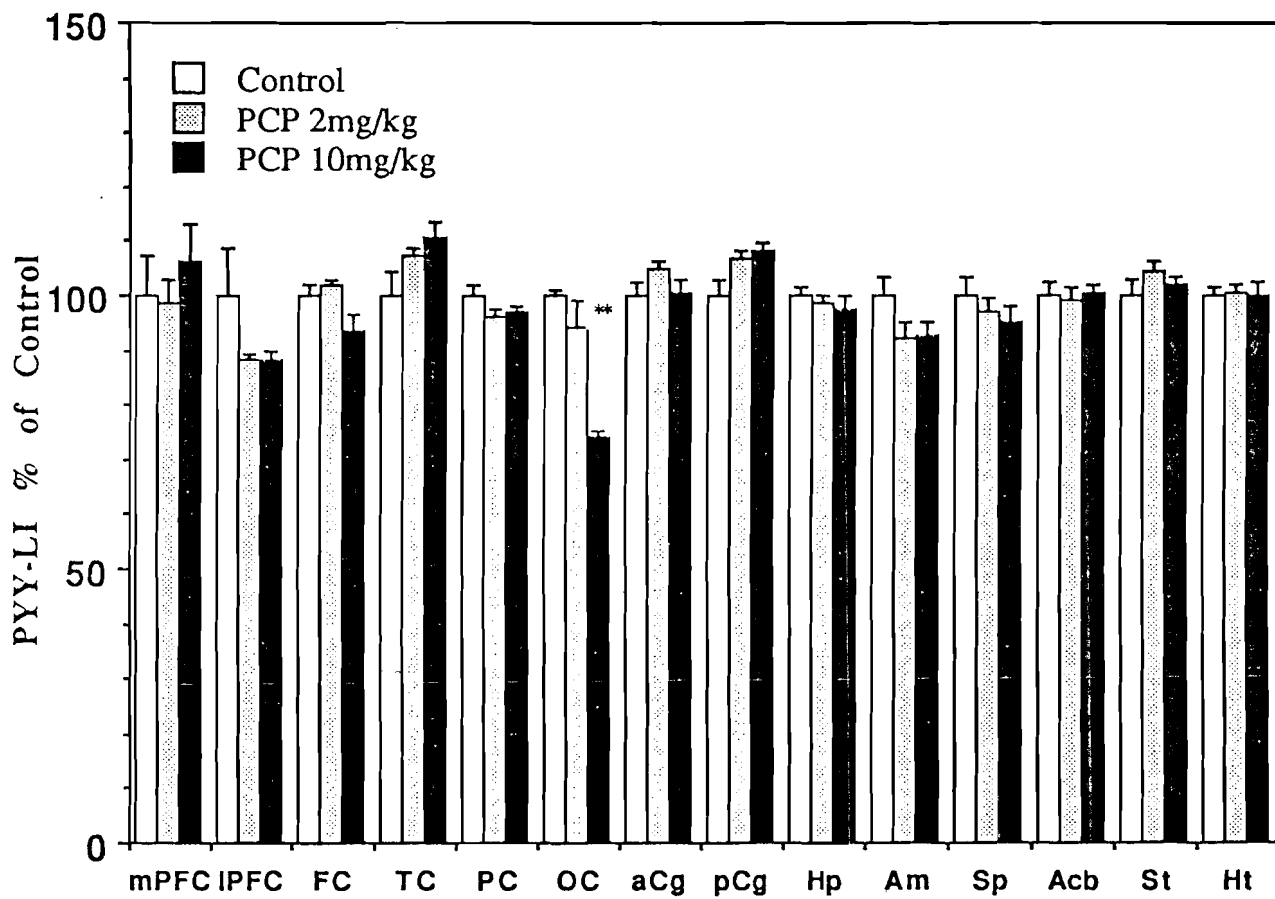


Fig 4

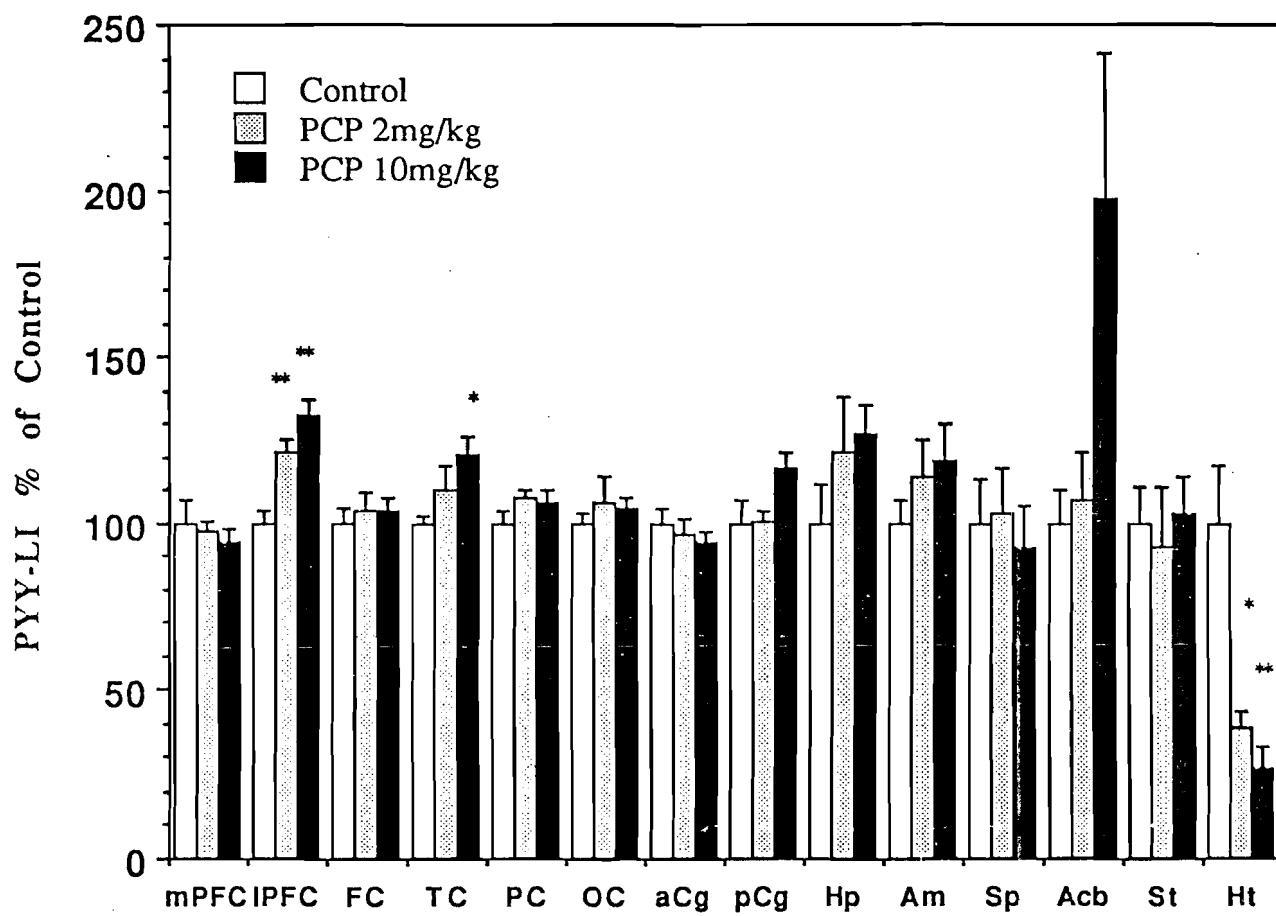


Fig 5

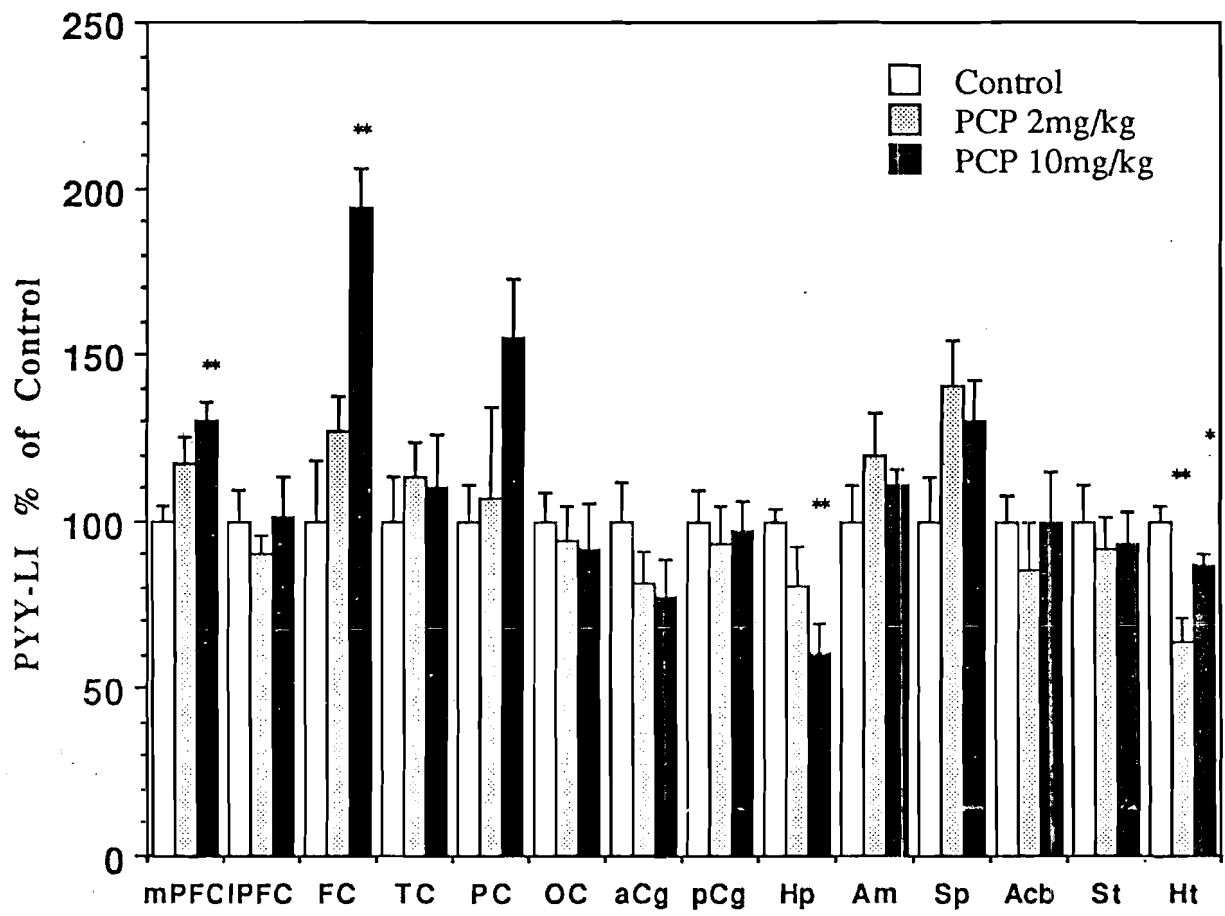


Fig 6