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Does neuropeptide Y (NPY) mediate the effects of psychotropic drugs?

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Abstract

Although several studies have summarized the effects of neuropeptide Y (NPY) in the central nervous system, its role in psychopharmacotherapy has not been reviewed in detail. For the last few years, there has been an increase in the number of studies on the suggested role of NPY in the benefits of treatment for mental disorders. Our review focuses on the possible involvement of altered NPY system activity in the effects of antianxiety, antidepressant and antipsychotic therapies. Potential sites and receptors, which are implicated in mediating the NPY effects of psychotropic drugs, have been described. We discuss the significance of alterations in the brain NPY system for the development of new methods of treatment for mental disorders.

Keywords: Neuropeptide Y (NPY); Anxiolytics; Antidepressants; Antipsychotic drugs; Central nervous system; Animal studies; Clinical data

1. Introduction

Neuropeptide Y (NPY), a 36 amino acid peptide belonging to the pancreatic polypeptide family, is one of the most abundant and widely distributed peptide in the central and peripheral nervous systems of humans and many animals [1]. In the central nervous system (CNS), NPY acts as a neurotransmitter/neuromodulator, and its effects are mediated by specific receptors, such as Y_1, Y_2, Y_4, Y_5, and y_6 [2,3]. In CNS, NPY is involved in the regulation of many physiological functions. The best known effects of NPY in the brain are as follows: stimulation of food intake, anxiolytic action, regulation of synthesis and secretion of several hormones, anticonvulsant effect, central regulation of the cardiovascular system, modulation of cognitive functions, and control of circadian rhythms [1,4–6]. Behavioural observations of NPY knockout mice suggest that NPY plays an important role in reducing CNS hyperexcitability. NPY knockouts occasionally exhibited spontaneous seizures, were more sensitive to excitotoxicity provoked by a γ-aminobutyric acid (GABA) antagonist or glutamatergic agonist, and displayed increased anxiety in the passive avoidance and elevated plus maze test [7].

Although several reviews on the function of NPY in CNS have been published, none of them describes in detail the role of NPY in the mechanism of action of psychotropic drugs. Therefore, in this review, we focus on the effects of these drugs on NPY system activity and on the potential role of these effects in the treatment of anxiety, depression and psychotic disorders.

2. NPY and pharmacotherapy of anxiety

2.1. NPY and anxiety

NPY, when administered intracerebroventricularly or intrastructurally, produced an anxiolytic-like effect in such animal anxiety models as the elevated plus-maze [8,9], the Vogel test [8], the fear-potentiated startle [9], the Geller–Seifter conflict test [10] and the social interaction test [11,12]. The anxiolytic effect of NPY results mostly from the stimulation of Y_1 receptors [1,12–14] and, probably also, but to a lesser extent, from the stimulation of Y_5 receptors [15]. Activation of Y_2 receptors produces anxiety-like behaviour resulting probably from decreased release of endogenous NPY [16–18]. Exposure to stress alters NPY system activity in many brain regions such as the amygdala,

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Table 1
Effect of stress on NPY system in rat brain

Model of stress/fear	Strain of rats	Results	Reference
Amygdala			
Restraint stress	Wistar–Kyoto rats	A 50% increase in medial amygdala NPY mRNA after 3 days of restraint	[19]
Conditioned fear produced in the passive avoidance test	Sprague–Dawley rats	A 33% increase in NPY-LI 6 h after the test	[20]
Restraint stress	Sprague–Dawley rats	NPY mRNA levels decreased by 30 and 35%, 1 and 2 h after acute restraint, respectively. NPY-LI decreased by 25% 1 h after acute restraint	[21]
Hypothalamus			
Restraint stress	Wistar–Kyoto rats	Arcuate nucleus NPY mRNA increased by 81 and 40% after 1 and 3 days of restraint, respectively	[19]
Conditioned fear produced in the passive avoidance test	Sprague–Dawley rats	A 19% increase in NPY-LI 6 h after the test	[20]
Restraint stress	Sprague–Dawley rats	A 23% increase in NPY-LI 10 h after acute restraint. No changes in NPY mRNA	[21]
Cerebral cortex			
Conditioned fear produced in the passive avoidance test	Sprague–Dawley rats	A 21% decrease in frontal cortex NPY-LI 6 h after the test	[20]
Restraint stress	Sprague–Dawley rats	Neocortex NPY mRNA levels decreased by about 35 and 45% 2 and 4 h after acute restraint, respectively. No changes in NPY-LI	[21]
Nucleus accumbens			
Conditioned fear produced in the passive avoidance test	Sprague–Dawley rats	A 22% increase in NPY-LI 6 h after the test	[20]
Hippocampus			
Restraint stress	Wistar–Kyoto rats	A 26% decrease in NPY mRNA after 10 days of restraint stress	[19]
Striatum			
Restraint stress	Sprague–Dawley rats	A 29% increase in NPY mRNA 2 h after acute restraint. No changes in NPY-LI	[21]

hypothalamus, hippocampus, cortex, nucleus accumbens and striatum [19–21] (Table 1). Studies with Y_1 receptor antisense oligonucleotides [13], Y_1 receptor antagonists [14,22,23], and NPY knockout mice [7] indicate that NPY is an endogenous anxiolytic and that attenuation or inhibition of NPY transmission is accompanied by anxiety. It seems that the amygdala NPY system [13] and probably the NPY systems in the periaqueductal grey matter [23], locus coeruleus [24] and dorsocaudal lateral septum [12] are involved in the regulation of fear and anxiety.

Human studies have shown that acute uncontrollable psychological stress significantly elevates plasma NPY levels, which were positively correlated with increased cortisol and norepinephrine concentrations. Enhanced NPY release was associated with less psychological dissociation, suggesting, in the authors' opinion, that NPY exhibits anxiolytic activity during stress [25]. Increased NPY levels were detected in patients with chronic panic disorder, who were drug-free for at least one week and had several panic attacks within one week before the procedure [26].

2.2. NPY and anxiolytic drugs

The colocalization of NPY and GABA in the neurons of amygdala [27], hypothalamus [28] and cerebral cortex [29], and direct synaptic contacts between GABA- and NPY-containing neurons in the amygdala [30] and nucleus accumbens [31], suggest that NPY may be involved in the action of anxiolytic drugs that stimulate $GABA_A$ receptors. This hypothesis is supported by two behavioural studies, which showed that NPY and benzodiazepines interact in the regulation of anxiety [14,16]. Diazepam prevented the decrease in the time spent in the open arms of the elevated plus-maze induced by the NPY Y_1 receptor antagonist BIBP 3226 [14]. Alprazolam reduced anxiogenic-like behaviour caused by the Y_2 receptor agonist C2-NPY in the social interaction test [16]. Our studies showed that the drugs with different mechanisms of action and pharmacological effects, given in anxiolytically effective doses, altered neuropeptide Y-like immunoreactivity (NPY-LI) levels in naive rats [32] (Table 2) and in rats with conditioned fear produced in the passive avoidance test [20] (Table 3). The latter finding seems to be particularly interesting because the animal models of CNS disturbances provide more informative data. Rats subjected to conditioned fear exhibited increased NPY-LI levels in the amygdala, nucleus acccumbens, and hypothalamus and decreased NPY-LI in the frontal cortex [20]. These changes were blocked by diazepam and attenuated by buspirone. The effect of diazepam on brain NPY-LI levels resulted from the stimulation of the benzodiazepine receptor as it was prevented by the benzodiazepine receptor antagonist flumazenil [20]. Naive rats showed rather slight changes in NPY-LI, mainly after multiple administration [32]. Compared to naive rats, those with conditioned fear [20] exhibited stronger (induced even by a single dose) and unidirectional effects of diazepam and buspirone in all brain regions studied. The differences in the effects of diazepam and buspirone on