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Review

Behavioral profiling of NPY in aggression and neuropsychiatric diseases

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ABSTRACT

The abundantly expressed neuropeptide Y (NPY) has potent effects on feeding, body weight, and blood pressure, and exhibits important functions in various behavioral domains such as motor activity and anxiety. The potent neurotransmitter exerts its biological effects through at least five G-protein coupled receptors termed Y_1, Y_2, Y_4, Y_5, and y_6. The behavioral profile of NPY function has been extensively studied using traditional pharmacological and classic genetic animal models. Based on these studies, variations in the profile of NPY and its receptors have been found. To limit the variability and inconsistencies in the behavioral profile of NPY and to clarify its effects on certain domains in further detail, it is important to design a rational standardized strategy for behavioral testing, using a complement of different well-established and reproducible tests. This strategy can minimize the risk that false positive or false negative results lead to a contradictory and inconsistent behavioral characterization of NPY function. Ideally, such screening should be composed of an initial monitoring of general health, sensory functions, and motor abilities, before specific behavioral domains such as anxiety or aggression are investigated using a multi-tiered phenotyping approach. In this review, we will focus on a brief description of the latest insights into the behavioral profile of NPY in the selective lesser investigated domains such as aggression and depression–schizophrenia-related behaviors. We will combine this information with possible strategies to evaluate the different specific phenotypes in more detail.

Contents

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1. Strategies in behavioral NPY research

Since its discovery in 1982 [87], neuropeptide Y (NPY) has been characterized as one of the most abundantly expressed peptides in the mammalian nervous system. Initial research discovered NPY's effect on feeding, body weight, and blood pressure [100]. More recent work focusing on behavior has revealed important functions of this neuropeptide in various domains such as motor activity, anxiety, learning and memory, aggression, seizure and ethanol susceptibility, ethanol consumption, circadian rhythm, and nociception. Even behaviors related to neuropsychiatric disorders (i.e. depression and schizophrenia) seem to be modified by NPY. The potent neurotransmitter exerts its biological effects through at least five G-protein coupled receptors termed Y_1, Y_2, Y_4, Y_5, and y_6.

The behavioral profile of NPY function has been studied extensively using traditional pharmacological and classic genetic animal models. A variety of (ant)agonists are available for the different Y-receptors (for details see [27]) although to date only a few of these compounds are highly specific (mostly for Y_1 and Y_2 receptors). Issues of low selectivity, solubility, toxicity, and other side effects limit the utility of some of the Y-receptor (ant)agonists in behavioral phenotyping [89], although newer agents such as the Y_1 antagonist J-115814 are highly specific and more effective at profiling the effects of NPY and its receptors [46]. Importantly, when using these compounds, the mode of administration itself has an impact on the behavioral performance of laboratory test animals. Thus, the development of genetic animal models was important for the *in vivo* behavioral profiling of NPY function. Nowadays, different mouse germline and inducible/conditional knockout and germline double knockout models for NPY and its Y-receptors are available for behavioral phenotyping. In addition, transgene animal models overexpressing NPY have been developed in the last few years for both *Mus musculus* and *Rattus norvegicus* (for overview see [60]). Using classic genetic animal models avoids the disadvantages/complications described for pharmacological strategies but at the cost of possible genetic background and compensatory mechanisms [28,59,70], which have already been found in some of these models (e.g. in NPY deficient mice: [93]). In the long term, the inducible/conditional knockout models will avoid most of the difficulties mentioned above but at present, few models are available for the different Y-receptors.

Importantly, variations in the behavioral profile of NPY and its receptors have been found in studies using transgenic versus pharmacological models and in investigations using similar Y-receptor knockout models developed by different investigators [60,70]. Indeed, some of the differences between pharmacological and genetic strategies appear to be species-specific as most pharmacological studies use rats as test animals, whereas genetic studies typically focus on mouse models [33,70]. To limit the variability and inconsistencies in the behavioral profile of NPY function and to clarify its effects on certain domains in further detail, it is important to design a rational standardized strategy for behavioral testing, using a complement of different well-established and reproducible tests (for an overview see Table 1). This strategy can minimize the risk that false positive or false negative results lead to a contradictory and inconsistent behavioral profiling of NPY. Ideally, such screening should be composed of an initial monitoring of general health, sensory functions, and motor abilities, before specific behavioral domains such as anxiety or aggressive-like behaviors are investigated using a multi-tiered phenotyping approach [15,17,51]. The philosophy of a multi-tiered test strategy is based on the fact that not all animal models for anxiety are equivalent in terms of the elicited/induced emotional state and that aggressive behavior has a non-unitary nature [76]. For example, a general screening of anxiety-related behaviors should include conditioned (e.g. conflict paradigms or active/passive avoidance) and unconditioned (e.g. exploration tests, social paradigmes, or antipredator tasks) response tests to screen different aspects of anxiety (for more details see: [76]). Similarly for aggression, there are different animal models targeting various forms of aggressive behavior (e.g. maternal, spontaneous, or territorial aggression-for overview see: [63]). Therefore, it is important to select the most appropriate (i.e. hypothesis-driven) tests for your research to avoid repetitive non-specific testing across models, which can lead to confusing and contradictory results.

It is well-accepted that a variety of factors such as breeding conditions [24], age of test animals [48], nutrition [7], single or group housing [91], environmental enrichment [68,95], circadian rhythm [47,56], and stress arousal during handling (e.g. caused by administration of pharmacological compounds or cohort removal effects: [49,53]) have a significant impact on a variety of behavioral parameters. Controlling for such effects is extremely important as NPY itself is involved in some of these factors (e.g. circadian rhythm and endogenous stress protection: [33,62]).

Thus, phenotyping strategies have to be designed very carefully and highly standardized to achieve accurate insights into the regulatory impact of NPY on behavior, as well as to allow comparison to earlier investigations and to minimize the overall impact of external factors on the animal's performance. In addition, the behavioral paradigms used must have demonstrated validity across many domains (predictive, face, and construct validity), to ensure appropriate study outcomes. In this review, we will focus on a brief description of the latest insights into the behavioral profile of NPY function in the

Table 1 – Overview — reviews for behavioral phenotyping

Phenotyping strategies	[13–19,43,51,77,88]
Genetic background phenotyping	[17,21,28]
Problems of behavioral phenotyping	[13,14,71,83,88,98,99,105]

Table 2 – Overview — NPY's role in aggression, depression, and schizophrenia	
Aggression	[25,50,52,54,78]
Depression	[2,3,8–12,23,30,33,35, 37–39,41,45,58,65,66,69,74, 75,78,80,85,89,91,94,101,102]
Schizophrenia	[3,9,10,22,26,42,44,52,58,65,67, 72,81,100,102]

selective domains aggression and depression-/schizophrenia-related behaviors (for an overview see Table 2) and combine this information with possible strategies to evaluate the different specific phenotypes in more detail.

2. Aggression

High immunoreactivity (IR) of NPY can be found in brain regions which are known to be involved in regulating aggression in mammals [31], such as the olfactory bulb, the hypothalamus, and the amygdala [55]. This IR profile suggests a role for NPY in aggression. The olfactory bulbectomized (OB) rat model provides further evidence for a potential involvement of NPY in aggression. This animal model, which is characterized by depressive-like behaviors and increased muricide (mouse-killing behavior), exhibits high concentrations of NPY in the medial amygdala [78]. The first real evidence for NPY's regulatory role in aggression originated from a pharmacological study reporting that NPY injected into the medial amygdala in combination with a low ineffective dose of noradrenaline dose-dependently suppresses muricide in 80% of OB rats [54]. An impact of sedative-like effects of NPY on the behavioral performance of OB rats was ruled out, as treatment with similar doses of NPY in control animals had no effect on muricide. Another study demonstrated that Y_1 antagonists reduce fighting in an apomorphine-induced aggression paradigm. This finding suggests that modulation of postsynaptic dopaminergic responses is responsible for this effect, rather than the direct influence of Y_1 receptor blockade on dopamine or NPY release [52]. In a genetic animal model for the Y_4 receptor, male Y_4 knockout mice displayed elevated aggressive behavior in the home cage [79]. The first comprehensive screening for an aggressive-like phenotype using a Y_1 receptor knockout model revealed that a lack of this Y-receptor attenuates territorial aggression by modulating serotonergic (5-HT) neurons in the raphe nucleus [50]. The interaction between NPY signaling and serotonergic mechanisms of aggression is likely to be mediated via a 5-HT_{1A} receptor pathway.

NPY plays a significant role in the incidence of aggression and has an important modulatory role in linking aggression circuits located in the limbic system (olfactory bulbs, amygdala, and hypothalamus), the prefrontal cortex, and the periaqueductal gray to feeding pathways located in the paraventricular and arcuate nuclei of the hypothalamus (for details see [25]). The involvement of other Y-receptors needs to be evaluated.

2.1. *Recommended behavioral phenotyping strategy*

The most commonly used aggressive paradigms are the Resident–Intruder (RI) test (for territorial aggression), the spontaneous aggression test, and the isolation-induced aggression task. A combination of these tests is recommended although it is important to remember that prior fighting experience and the dominance hierarchy within the home cage have a significant impact on aggression. Consequently, group-housing and repeated testing of an animal can complicate the interpretation of results [1,82]. Furthermore, a sensible standardization of experiments is important; for example, group-housed animals should not be tested on the day of cage cleaning, as this induces fighting between cage mates. Housing conditions must also be standardized as the level of home cage enrichment could influence territory values, which can affect fighting intensities in the RI test. It is also important to select the standard opponent carefully, as only the test animal should induce aggressive behavior. For example, mice of the inbred A/J strain are good standard opponents as these mice do not initiate aggressive encounters themselves and they rarely react aggressively when attacked. As anxiety [57], activity levels [61], and olfactory abilities [86] influence aggressive phenotypes, test animals should not only be observed in aggression paradigms but should also be screened for anxiety (using e.g. elevated plus maze, social interaction, and light dark test), motor activity (using e.g. open field testing and circadian rhythm measurements), and olfaction (for different test designs see [104]).

3. Neuropsychiatric diseases

3.1. *Depression*

Symptoms of anxiety and depression commonly coexist and both disorders are thought to reflect maladaptive changes in stress–response systems [40]. As extensive evidence exists for a role of NPY in stress and anxiety, it is not surprising that there are several studies suggesting that NPY has some regulatory function in depression as well [33,75]. Altered levels of NPY have been found in the plasma [66] and cerebrospinal fluid (CSF) of depressive [102] and suicidal patients [101], and reduced NPY levels were found in the prefrontal cortex of bipolar patients [10]. Some of these findings were not replicated in subsequent studies [3,69] but more recent experiments with improved techniques support the original results [37]. Similar alterations can be found in two animal models for depression, the OB rat [39,84], where NPY treatment rescued the ''depressed'' phenotype of these rats, and the Flinders sensitive rats [11,45]. Furthermore, CSF levels of NPY correlate negatively with anxiety scores in depressed patients. This may indicate that low concentrations of NPY predisposes to anxiety- or stress-related depression [36]. Support for such a correlation comes from animal studies using rats overexpressing NPY in the hippocampus. These transgene animals exhibited decreased anxiety levels [90].

Biochemical analyses have revealed that NPY and its receptors are highly expressed in the amygdala and the hypothalamus, brain areas, which participate in regulating/inducing emotionality and mood disorders [55]. In addition, NPY is co-expressed with noradrenaline, which is affected by antidepressant drug therapy [92].

Animal studies provide further evidence for the involvement of NPY in depression. Therapies such as antidepressant drug treatment (i.e. imipramine, fluoxetine, or lithium) or electroconvulsive shocks increase NPY-like immunoreactivity in the hypothalamus and hippocampus in rodents [8,34,41,96]. NPY also has a direct antidepressant-like effect in depression models such as the Porsolt swim test [75,85] and the OB rat [54]. These antidepressant properties of NPY seem to be mediated via the Y_1 receptor [54]. Interestingly, the Y_2 receptor also plays a role in NPY's antidepressant potential, as the inactivation of Y_2 receptors leads to an antidepressant-like phenotype in mice [94]. The pharmacological findings of antidepressant-like effects of NPY have mostly been obtained following acute NPY administration in ''non-depressed'' animals. However, further evidence is required to establish whether central administration of NPY will also be able to rescue ''depressed'' phenotypes other than the OB rat.

Importantly, core symptoms of depression are linked to dysfunctional regulatory processes within the hypothalamic-pituitary-adrenal (HPA) axis. These symptoms are characterized by sleep disturbances, anxiety, and loss of appetite. NPY is known as a major player in all these domains [32,35,100]. Furthermore, central NPY administration significantly affects plasma adrenocorticotropic hormone and glucocorticoid hormone expression [2,97] and therefore the HPA axis.

3.1.1. *Recommended behavioral phenotyping strategy*

Behavioral models for depression are basic approaches to detect depressive-like behaviors rather than sophisticated paradigms covering all the different aspects of this mental disorders. In depression, the most commonly used non-lesion tests are the tail suspension test, the Porsolt swim test, learned helplessness, and drug-withdrawal-induced anhedonia [16,20]. The Porsolt swim test is probably the most commonly used paradigm, in which a test animal has to swim in an inescapable water-filled cylinder for 10 min (day 1) and 5 min (day 2). The time the animal stays immobile is recorded. The theoretical validity of this model is based on the assumption that the test animal becomes desperate as it learns that escaping the cylinder is impossible [73]. Importantly, the animal's behavior during exposure to the dangerous situation depends upon previous knowledge of the environment. Therefore, the behavioral immobility is probably caused by an awareness of danger in a familiar environment rather than by ''behavioral despair'' and is dependent on pre-exposure of the animal to a stressful situation [4,6]. Thus, the Porsolt swim test is far from reproducing the behavioral changes that characterize depressive illness in humans [5] — even more as antidepressants reduce immobility time after acute treatment, whereas the clinical time course of antidepressant action normally requires 3–4 weeks [6,103]. Importantly, an animal model of depression (i.e. bulbectomized rats) behaves like a control group in the Porsolt swim test [29]. Thus, if using this test, at least the full repertoire of animal behavior should be analylsed in addition to the recording of the duration of behavioral immobility. Nevertheless, most researchers now a days agree that basic paradigms such as the tail suspension test and the Porsolt swim test must be combined with other depression models such as chronic mild stress procedures (cold water swimming, handling stress, restraint stress: [103]) or less preferable lesion models such as OB rats [20,103].

3.2. *Schizophrenia*

The role of NPY in schizophrenia has only been discussed in the last two decades. Several biochemical analyses have demonstrated an obvious influence of NPY on schizophrenia, as altered NPY levels were found in the temporal cortex [26] and CSF [102] of schizophrenia patients. Support for a NPY-related model of neurodevelopmental dysfunction in schizophrenia comes from findings that the proportional distribution of NPY-positive neurons as well as fibers (their compositional ratio in upper/lower cortical layers and subcortical/deep white matter) differs between schizophrenia patients and healthy individuals [42]. Other studies have demonstrated a decrease in NPY gene expression in schizophrenia subjects accompanied by a significant reduction of NPY mRNA levels in the frontal cortex [58]. Importantly, in humans, a polymorphism in the promoter region of the NPY gene is associated with schizophrenia, as the −485T allele in the NPY gene may confer susceptibility to schizophrenia by decreasing NPY levels in the brain [44].

NPY is also implicated in schizophrenia therapy: some psychopharmacological substances target the NPY system by modifying the endogenous levels of this neuropeptide: e.g. treatment with the typical antipsychotic haloperidol results in the elevation of cortical NPY levels in schizophrenia patients and also animal models for schizophrenia [72,81]. Changes in the NPY system may contribute both to the therapeutic power and related side effects of such antipsychotics [67]. Interestingly, single or multiple injections of phencyclidine (PCP), one of the major drug models for schizophrenia as it induces a broad spectrum of schizophrenia-like symptoms, decreases NPY levels in the striatum, a brain area that is crucial in the etiology of schizophrenia [64].

Importantly, the Y_1 receptor is highly expressed in schizophrenia-affected regions such as the dentate gyrus of the hippocampus and the medial amygdala [55]. Y_1 receptor activation also inhibits the behavioral response to a core feature of schizophrenia, the dopaminergic stimulation [52].

3.2.1. *Recommended behavioral phenotyping strategy*

As in depression research, the behavioral models used to detect schizophrenia-like behaviors are rather simple and not specific or standardized between different laboratories. In schizophrenia research so far, the focus has been on examining sensorimotor gating deficits (similar phenomenon in humans and rodents) and hyperactivity in potential animal models for this complex disorder. In addition to testing animal models in the prepulse inhibition and the open field tests, which are not highly specific only for schizophrenia, other paradigms related to olfaction (olfactory discrimination or social transmission food preference), learning and memory (latent inhibition, spontaneous alternation task, passive avoidance, and a spatial memory task such as Barnes maze), and social attention (RI test or social interaction) should be included (to target not only positive but also negative symptoms of schizophrenia).

In summary, there is good evidence that NPY is involved in the etiology and pathophysiology of neuropsychiatric illnesses such as depression and schizophrenia. It is likely that these illnesses are related to altered expression of NPY and/or differential processing of NPY. The potentiation of NPY signaling, primarily at the Y_1 receptor might offer an attractive target for novel treatments of affective disorders [35,75]. It is possible that at least some of the effects of NPY on behavioral parameters linked to neuropsychiatric diseases are mediated by normalizing the catecholaminergic, dopaminergic, and serotonergic systems in the brain and peripheral HPA function.

4. Summary

Since its discovery in 1982, NPY has revealed important functions in behavioral domains including motor activity, anxiety, nociception, and learning and memory. In this review, we have summarized the latest outcomes for the behavioral profile of NPY in less well investigated behavioral domains such as aggression and neuropsychiatric illnesses and have discussed possible and sensible phenotyping strategies for these domains. Furthermore, it is very important to decide what animal model (pharmacological versus genetic, germline knockout versus conditional knockout) to use to investigate these domains. In the long term, the use of conditional knockout models will be the most valuable tool, unless more specific (ant)agonists with fewer side effects are developed. The detailed investigation of NPY's regulatory function in depression and schizophrenia will be particularly important for the discovery and development of potential new therapies and treatment targets.

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