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Neuropeptide Y: A stressful review

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Abstract

Stress is defined as an adverse condition that disturbs the homeostasis of the body and activates adaptation responses. Among the many pathways and mediators involved, neuropeptide Y (NPY) stands out due to its unique stress-relieving, anxiolytic and neuroprotective properties. Stress exposure alters the biosynthesis of NPY in distinct brain regions, the magnitude and direction of this effect varying with the duration and type of stress. NPY is expressed in particular neurons of the brainstem, hypothalamus and limbic system, which explains why NPY has an impact on stress-related changes in emotional-affective behaviour and feeding as well as on stress coping. The biological actions of NPY in mammals are mediated by the Y1, Y2, Y4 and Y5 receptor, Y1 receptor stimulation being anxiolytic whereas Y2 receptor activation is anxiogenic. Emerging evidence attributes NPY a role in stress resilience, the ability to cope with stress. Thus there is a negative correlation between stress-induced behavioural disruption and cerebral NPY expression in animal models of post-traumatic stress disorder. Exogenous NPY prevents the negative consequences of stress, and polymorphisms of the NPY gene are predictive of impaired stress processing and increased risk of neuropsychiatric diseases. Stress is also a factor contributing to, and resulting from, neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's disease, in which NPY appears to play an important neuroprotective role. This review summarizes the evidence for an implication of NPY in stress-related and neurodegenerative pathologies and addresses the cerebral NPY system as a therapeutic target.

Keywords

Anxiety; neurodegenerative diseases; neuropeptide Y; post-traumatic stress disorder; stress; stress-induced feeding changes; stress resilience; Y1; Y2; Y5

1 NPY and its receptors

Neuropeptide Y (NPY) is a 36-amino acid peptide which belongs to the so-called NPY family of biologically active peptides, together with two other members, peptide YY and pancreatic polypeptide (PP) (1). Originally NPY was isolated from brain extracts (2) and found to be one of the most abundant neuropeptides within the brain (3). NPY has a pivotal role in many physiological functions such as food intake, energy homeostasis, circadian

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rhythm, and cognition (4–7). In addition, the peptide has been suggested to be a key component in the stress response, having anxiolytic properties (3,8).

The numerous and diverse NPY effects are related to its expression in a multitude of brain areas. Mapping studies investigating NPY mRNA production within the rodent brain identified 4 regions as the main sources of cerebral NPY synthesis (9). These regions include the hypothalamic arcuate nucleus (ARC), the locus coeruleus (LC), the nucleus tractus solitarii (NTS) and the septohippocampal nucleus (9). NPY is, in addition, present in many cortical interneurons, amygdala, hippocampus, nucleus accumbens (NAc), periaqueductal gray, basal ganglia and thalamus (1,9). An important fibre tract containing NPY exists between the ARC, a major source of NPY, and the paraventricular nucleus of the hypothalamus (PVH), the major source of corticotropin-releasing hormone (CRH), allowing a crosstalk between these two neuropeptide systems (10).

To date seven different Y receptors (Y1-Y8) have been described in vertebrates, of which up to 5 (Y1, Y2, Y4, Y5, y6) are present in mammals (11). While the Y1, Y2, Y4 and Y5 receptors are functional in all mammals, the y6 receptor is non-functional in several mammals including humans and has been lost in rats (12). The receptor originally identified as the Y3 receptor has been characterized as CXC chemokine receptor type 4 and is thus included in the chemokine receptor family (13). NPY shows strong affinity for the Y1, Y2 and Y5 receptor, while PP is the preferential agonist at the Y4 receptor (13). Like NPY itself, the Y1 and Y2 receptors are widely distributed throughout the brain. Brain areas expressing Y1 and Y2 receptor immunoreactivity include the frontal cortex, lateral septum, NAc, bed nucleus of the stria terminalis, PVH, ARC, lateral hypothalamus, amygdala, hippocampus, NTS and area postrema (9,14,15). In contrast, Y4 receptor expression is restricted to only a few brain regions including the medial preoptic area, PVH, NTS and area postrema (9). Finally, the Y5 receptor occurs in several limbic brain areas but is less abundant than the Y1 or Y2 receptor (16,17). Interestingly, Y5 receptor expression coincides in most cases with Y1 receptor expression, but not vice versa (18,19).

2 Role of NPY in stress processing

Stress is a term deeply rooted and frequently used in everyday language. Originally described as acute nonspecific nocuous agents affecting the body by Hans Selye in the 1930s (20), stressors are now defined by their ability to disturb homeostasis (21). These disturbances are detected by the sensory systems and the information is transmitted to the brain. Depending on the magnitude of homeostatic alterations, the perception of stress activates adaptation systems. A number of reports indicates that NPY is crucial for the stress adaptation process, besides other major biological pathways such as the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system. Accordingly, a concept has been developed, which implicates NPY in the termination of the stress response and its interaction with the HPA axis (22). This concept holds that NPY counteracts the biological actions of CRH, a 41-amino acid neuropeptide which is transcribed and released upon stress exposure in the PVH (23). On the behavioural level, stress-induced CRH expression, CRH overexpression as well as central CRH administration have been found to induce anxiety in rodents (24). In contrast, NPY, the functional counter player of CRH, has anxiolytic effects.

Intracerebroventricular (icv) administration of NPY renders mice less anxious (25), an effect that is also seen after NPY injection directly into the amygdala or hippocampus, indicating that these regions are key regions in the anxiolytic effect of the peptide (26,27). The findings that NPY knockout mice are more anxious, and hippocampal or amygdalar NPY overexpression renders animals less anxious, confirm the anxiolytic properties of endogenous NPY and the importance of the limbic system in this effect (28–31).

Stress potently influences NPY expression in the brain, but the magnitude and even the direction of stress-induced NPY alterations heavily depend on the type and duration of stress, time point of NPY measurement as well as brain region examined (Table 1). For instance, NPY gene expression in the amygdala, a brain region important for the processing of fear and anxiety, is increased after footshock stress (32), unaltered by acute water avoidance stress (WAS) (33), but decreased by acute restraint stress (34). These findings indicate that the type of stressor has a large influence on the reaction of the NPY system in this brain area. A similar variability in amygdalar NPY expression has been observed with chronic stress paradigms (35–38).

As regards NPY expression measured across the whole hypothalamus or within the ARC, most evidence attests to increased NPY transcription after exposure to acute stressors (33,36,39–42) but not chronic stress paradigms (35,38,43), indicating habituation after repeated stress exposure. However, the pertinent evidence is somewhat contradictory as acute air puff stress does not change hypothalamic NPY expression whereas 3 days of restraint stress elevates NPY in the ARC (36,43). Importantly, the changes in NPY expression in the hypothalamus depend on the interval between stress exposure and measurement, as is evident from the data shown in table 1.

Like in the hypothalamus, the kind and duration of stress is decisive for its effect on the NPY system in the hippocampus. While WAS does not change hippocampal NPY transcription, acute restraint stress and Morris Water Maze training increase, whereas chronic restraint stress decreases NPY mRNA levels in the hippocampus (33,36–39). Likewise, NPY expression in the LC is increased, unaltered or decreased, depending on the type and length of stress exposure (32,36,43).

Besides its sensitivity to external stressors, cerebral NPY expression is also affected by the internal stress of visceral inflammation. For instance, trinitrobenzene sulfonic acid-induced colitis, an animal model of Crohn’s disease, increases the NPY concentration in brain and plasma (44). Furthermore, in mice with dextran sulfate sodium-evoked colitis, a model of ulcerative colitis, amygdalar and hippocampal NPY expression is decreased, while hypothalamic NPY production is increased (33,38). Especially the NPY changes within the limbic system are noteworthy since both colitis and the related disturbance of the microbiota-gut-brain axis induce behavioural changes which may involve NPY (1,45). However, not all experimental models of peripheral inflammation affect the central NPY system. Thus, after, Helicobacter pylori infection, the expression of NPY mRNA in the brain remains unaltered (46).

3 Role of NPY in anxiety

Increased anxiety is a distinct component of the stress response, with CRH exerting an anxiogenic effect that is counteracted by NPY-mediated anxiolysis (25–27). A number of reports indicates that the anxiolytic activity of NPY is primarily mediated by the Y1 receptor. For instance, intraamygdalar administration of the Y1 receptor antagonist BIBP 3226 is anxiogenic, while icv administration of a selective Y1 receptor agonist is anxiolytic (30,47). Direct pharmacological evidence corroborates that the anxiolytic effect of NPY is mediated by the Y1 receptor, since administration of a selective Y1 receptor antagonist before or together with NPY abolishes the anxiolytic effect (48,49). In line with these findings, conventional Y1 receptor gene knockout as well as selective Y1 receptor knockout in forebrain neurons are anxiogenic (50,51), while hippocampal Y1 receptor overexpression renders mice less anxious (52). This implication of Y1 receptors is contradicted by a study in which intraamygdalar administration of a Y1 receptor agonist failed to alter conditioned fear (53). Additionally, Y1 receptor antagonism did not prevent the anxiolytic effect of NPY, suggesting the involvement of other Y receptors.

In search for the biological relevance of Y1 receptor activation, the effect of NPY on the excitability of amygdalar neurons was investigated as a potential explanation for NPY-induced behavioural changes (54). The Y1 receptor agonist [Leu^{31},Pro^{34}]-NPY reduced the amplitude of NMDA-evoked excitatory postsynaptic currents but increased the amplitude of $GABA_A$ receptor-mediated inhibitory postsynaptic currents. This dual effect resulted in overall inhibition of amygdalar glutamatergic pyramidal neurons (54), which is consistent with the anxiolytic effect of NPY. Another mechanism whereby the Y1 receptor can influence anxiety involves calcineurin, a protein phosphatase, which is implicated in synaptic plasticity and shows high colocalization with the Y1 receptor in the basolateral amygdala (55). Cells expressing both the enzyme and the receptor are primarily pyramidal neurons and only to a small percentage interneurons. Antagonism of calcineurin activity prevents the long-term anxiolytic effect of NPY, suggesting an involvement of calcineurin-induced plasticity in the behavioural effect of NPY and a calcineurin-induced synaptic remodelling of pyramidal neurons in the basolateral amygdala (27,55).

In contrast to the Y1 receptor, stimulation of the Y2 receptor has an anxiogenic effect, which is related to the presynaptic localization of this receptor and its function as an autoreceptor reducing NPY release (56,57). For instance, NPY_{13-36}, a selective Y2 receptor agonist, increases the preference of mice for the closed arms of the elevated plus maze (EPM), which is consistent with anxiogenic behaviour (58). In line with this finding, icv or intraamygdalar blockade of the Y2 receptor with BIIE0246 (59,60) as well as intraamygdalar deletion of the receptor is anxiolytic (61). In addition, the brain-penetrant Y2 receptor antagonist JNJ31020028 has also anxiolytic properties. JNJ31020028 reverses the anxiogenic effect of alcohol withdrawal and nicotine-induced social anxiety-like behaviour (62–64). Surprisingly, conventional Y2 receptor knockout has yielded mixed results. While 3 studies observed antidepressant and antianxiety effects of Y2 receptor knockout, another study failed to confirm these findings (65–68). It has been suggested that the genetic background has a strong influence on the behavioural effects of Y2 receptor knockout and may be the reason for these divergent findings.

The role of the Y2 receptor in anxiety is further obscured by an anxiolytic effect of local Y2 receptor stimulation in the brain. Administration of NPY_{3-36} into the region of the LC increases entries to and time spent on the open arms of the EPM (69), and intraseptal infusion of the same compound increases open arm exploration and decreases the proportion of rats which bury in the shock-probe burying test (70). A potential explanation for these apparently paradox observations relates to brain-region dependent interactions of the Y2 receptor with major neurotransmitter systems. Thus, Y2 receptor activation has been described to inhibit the release of glutamate, GABA, dopamine and noradrenaline (68,71,72). It is hence conceivable that the behavioural effects of local Y2 receptor stimulation vary depending on the neurotransmitter repertoire of specific brain regions.

Data on the role of the Y5 receptor in anxiety are limited and controversial. The first study using a Y5 receptor antagonist failed to modify anxiety in the social interaction (SI) and EPM tests (73). However, two consecutive studies revealed an anxiolytic effect of a selective Y5 receptor agonist in the EPM, open field (OF) and SI tests (47,74). These discrepancies may not only be due to different selectivity of the Y5 receptor ligands but also to different interactions with other neurotransmitter systems of the brain. Quarta et al. (75) described that a Y5 receptor agonist enhances dopamine and noradrenaline release in the NAc and medial prefrontal cortex. The implication of the Y5 receptor in anxiety is further blurred by the anxiolytic effect of a selective Y5 receptor antagonist in the SI test (76). Genetic studies did not help to solve this riddle as both Y5 receptor knockout mice and mice with hippocampal or amygdalar Y5 receptor overexpression do not differ in anxiety tests (77,78). Recently it has been postulated that an interaction of the Y5 receptor with the Y1 receptor plays a role in regulating anxiety. Specifically, conditional knockout of the Y1 receptor in Y5 receptor-expressing neurons resulted in an anxiogenic phenotype of mice (79). In another study (80) it was demonstrated that this effect is reproducible and not affected by differential housing conditions (isolation vs. group housing). A small sample size human study provides preliminary support for an involvement of the Y5 receptor gene in panic disorder (81). Furthermore, the finding of a negative correlation between Y5 receptor mRNA in the central amygdala of rhesus monkeys and anxious temperament suggests a role of this receptor in the neural processes underlying temperament (82).

Relative to NPY and peptide YY, PP has the highest affinity for the Y4 receptor (13). In the first investigation on the role of the Y4 receptor in anxiety it was found that icv administration of PP altered food intake but not anxiety (83). In contrast, genetic deletion of the Y4 receptor has an anxiolytic effect in the OF, EPM and light-dark box tests (67,84,85). In addition, Y4 receptor knockout impairs fear extinction (86). The anxiolytic effect of Y4 receptor deletion is amplified by Y2/Y4 receptor double knockout, suggesting a positive interaction of Y2 and Y4 receptors (85). Unfortunately, the elucidation of the role of Y4 receptors in anxiety and other physiological functions is hampered by the lack of Y4 receptor-selective non-peptide antagonists. It is also unclear which endogenous agonist is acting via the Y4 receptor in the brain. There is little evidence that PP is produced in the brain, given that the immunoreactivity which was once believed to reflect PP turned out to be NPY (87,88). Accordingly, central NPY, although about 100 times less potent than PP in Y4 receptor activation (89,90), or peripheral PP crossing the blood-brain barrier (BBB) (91) are probably responsible for Y4 receptor-mediated effects on anxiety.

4 NPY as a mediator between stress and food intake

The HPA axis, a stress effector pathway, and food intake have been linked with each other, based on the findings of a glucocorticoid response to food intake and fasting-induced stimulation of the HPA axis (92). Since then a multitude of studies have suggested that stress alters food intake in a bidirectional manner since both stress-induced increases and decreases of feeding have been described (93). The direction of change depends on many factors such as the severity of stress and the levels of stress hormones (glucocorticoids, CRH, urocortin), metabolism-related hormones (leptin, insulin, ghrelin) and feeding-related neuropeptides (alpha-melanocyte stimulating hormone, agouti-related protein, melanocortins, NPY) (94).

In the central nervous system the interaction between stress and food intake is regulated by neuroanatomical pathways in the hypothalamus, in which NPY has a key role. As described above, hypothalamic NPY in the ARC is altered by a variety of stressors, and the projection of NPY neurons from the ARC to the PVH (10) allows for a crosstalk of the NPY system with the HPA axis in the course of stress. NPY itself is a potent orexigenic peptide (95), which suggests that stress-induced NPY increases lead to increased stress-induced food intake. In line with this idea, Krolow et al. (96) report that calorie consumption and hypothalamic NPY expression increase in male rats subjected to isolation stress. Furthermore, after a 30-min restraint stress period, food intake is lower in female NPY knockout mice compared to female WT mice, which suggests that stress-induced food intake depends on NPY (97). Similarly, food intake in female as well as male NPY knockout mice is decreased during a 4-hour exposure to novel environment stress (97).

It has been suggested that the orexigenic effect of NPY is primarily mediated by Y1 and Y5 receptors (6). In a stress setting this has been confirmed by Goebel-Stengel et al. (98) who report that acute tail pinch increases food intake in rats, an effect inhibited by the Y1 receptor antagonist BIBP-3226. However, there is also evidence for a role of the Y2 receptor in the interaction between stress and food intake. JNJ-31020028, a Y2 receptor antagonist, attenuates the effect of stress to reduce food intake in fasted rats (99). In contrast, to our knowledge, a potential role of the Y4 and Y5 receptor in the interaction between stress and feeding has not yet been disclosed.

Although the available evidence speaks for an involvement of NPY in the stress-feeding connection, the relation between stress, NPY and food intake is not as clear-cut as suggested above, because stress can increase or decrease food intake without accompanying NPY alterations. For instance, early life stress increases food intake and body weight in adult rats, but does not influence the hypothalamic NPY content (100). Likewise, chronic immobilization stress alters food intake and body weight gain in rats, which does not depend on NPY alterations in the ARC but is accompanied by increases in leptin and leptin receptor levels (101). In another study, acute restraint stress and forced swim stress have been found to reduce cumulative food intake, which is accompanied by an increase in hypothalamic proopiomelanocortin expression while NPY levels stay unaltered (102). Furthermore, acute crowding stress inhibits food intake in fish, but does not change central NPY expression (103).

These findings are at variance with other studies in which a stress-induced reduction of food intake is associated with increased NPY expression. For example, Melhorn et al. (104) report that in the visible burrow system, a rodent model of chronic social stress, food intake is decreased in both dominant and submissive animals compared to controls, with the submissive animals showing the largest feeding reductions. NPY expression in the ARC is enhanced in both submissive and dominant animals, which may be a counterregulatory mechanism to reverse the stress-induced diminution of calorie intake (104). In line with this finding, acute restraint stress in rats also reduces food intake and increases NPY expression in the PVH (105). Furthermore, heat stress suppresses food intake in chicken, which is associated with increased hypothalamic NPY mRNA expression (106).

In humans, chronic stress-induced increases in food intake can be detrimental as they may facilitate the development of pathological conditions such as obesity. Preclinical evidence indicates that NPY favours this transition via multiple effects. Specifically, NPY released from sympathetic nerves in the course of stress activates Y2 receptors on visceral white adipose tissue, which results in an increased growth of abdominal fat (107). Additionally, stress-induced glucocorticoid release, which increases hypothalamic NPY expression and food intake, may constitute a central mechanism as to how NPY promotes obesity (108). In another experimental setting, prenatal stress has been found to predispose the female offspring to diet-induced obesity in adulthood which is associated with a decrease in the hypothalamic expression of NPY (109).

5 Role of NPY in stress resilience: evidence from animal studies

The involvement of NPY in the stress reaction of the brain and its anxiolytic properties raise the question whether NPY also promotes stress resilience, the ability to cope with stress. Indeed, several lines of evidence attest to resilience-promoting properties of the peptide.

An initial study in transgenic rats with hippocampal NPY overexpression found that these animals are protected from the negative consequences of restraint stress (29). Precisely, the transgenic rats were insensitive to stress-induced anxiety on the EPM and did not show fear suppression in a punished drinking test. This finding is in line with another study which reported NPY as a resilience factor for restraint stress-induced behavioural disturbances. Repeated administration of NPY into the basolateral amygdala rendered mice resilient to stress as they were protected from the negative consequences of restraint stress in the SI test, an effect present for up to 8 weeks (27). A role for NPY in stress resilience was also corroborated through analysis of stress-induced disturbances of NPY expression in distinct brain regions (110). After chronic variable stress NPY peptide levels in the amygdala were reduced, while NPY levels in the prefrontal cortex were increased. These molecular changes may provide an explanation for the exaggerated fear response and delayed expression of fearful arousal seen in rats subjected to chronic variable stress (111). Interestingly, both reduced amygdalar NPY and increased prefrontal NPY synthesis may have the same functional consequence, namely to impair stress resilience. Attenuated NPY signalling in the amygdala has negative behavioural consequences (anxiety), and the increase of NPY formation in cortical interneurons may dampen the output from the prefrontal cortex, disinhibit the amygdala, and thus cause negative behavioural effects. Finally, NPY has also

been suggested as a key mediator of the resilience effect of repeated WAS which prevents behavioural disturbances due to experimental colitis (38). Repeated WAS, a psychological stressor for mice, reversed colitis-induced behavioural disturbances in the OF and SI tests, an effect associated with an increase in hypothalamic NPY mRNA. Although it is at first glance surprising that chronic stress is beneficial for mice suffering from colitis, it has been previously suggested that repeated mild predictable stress during adolescence can attenuate the behavioural response to stress in adulthood (112). Thus, the right daily “dose” of stress can be beneficial, may even be necessary to develop adequate coping strategies for unexpected traumatic events and may involve recruitment of the central NPY system.

Stress resilience has turned out to be an individual trait, which advocates the study of stress reactions in individuals in addition to group-based protocols. This translational approach is based on the aetiology and pathophysiology of post-traumatic stress disorder (PTSD). It is well established that the response of individuals to the same psychological trauma varies widely, ranging from severe psychological impairments to complete resilience. Although individual and environmental factors relevant for coping with traumatic events have been identified, appropriate animal models are necessary to uncover the biological basis of stress resilience (Figure 1).

To delineate individual differences in the behavioural stress reaction, Bardi et al. (113) investigated the coping style of rats during gentle restraint. To this end they quantified the number of escape bouts during 2 sessions of holding the rats in supine position for periods of 1 min. Active coping was defined as 7 or more escape trials during the test while passive coping was defined as six or fewer escape trials. Variable copers were defined as rats exhibiting passive coping during one test session and active coping in another session. Importantly, there was a correlation between the coping style of rats during gentle restraint and hippocampal NPY levels. Immunohistochemical analysis revealed that rats with a variable coping strategy had higher hippocampal NPY levels than rats with a passive or active coping style only (113). Moreover, variable copers exhibited a high level of adaptive responsiveness in three successive forced swim tests along with increased NPY levels in the amygdala and the bed nucleus of the stria terminalis (114). Behavioural flexibility in response to a stressful task may thus be a correlate of stress resilience mediated by NPY.

Cohen et al. (115) adopted a different model in which the behavioural reaction of rats to predator scent stress was used to evaluate individual stress coping. Based on cut-off behavioural criteria, animals were differentiated into an extreme behavioural response group, a partial behavioural response group and a minimal behavioural response group (115). Based on this paradigm, a correlation between behavioural disruption of animals after predator scent stress and brain NPY levels was disclosed (116). Animals whose behaviour was extremely disrupted had the lowest brain NPY levels. Treatment of animals with NPY shortly after stress exposure significantly reduced the prevalence of extremely disrupted behaviour while administration of the Y1 receptor antagonist BIBO3304 exaggerated behavioural disruption. These findings suggest that NPY acting via the Y1 receptor is a stress resilience factor (116). A consecutive study found that the behavioural and NPY response to predator scent stress in rats depends on the phase of the light/dark cycle (117). If stress was applied at the onset of the inactive phase (light phase), rats were more anxious

and displayed more disruption of behaviour than rats exposed to stress at the onset of the dark phase. NPY and Y1 receptor immunoreactivity decreased in response to stress in the PVH and ARC, a change that was more pronounced in rats stressed at the onset of the light phase, indicating a circadian influence on the stress-induced disruption of the NPY system (117). NPY administration before stress exposure had an anxiolytic effect, which was accompanied by upregulation of NPY and the Y1 receptor in the brain (117). In another study from the same group NPY was also implicated in the resilience effects of physical exercise (118). Rats which underwent a 6-week treadmill training before predator scent stress exposure did not suffer from the adverse behavioural consequences of the stressor (reduced time spent on the open arms of the EPM, increased acoustic startle response). This exercise-induced behavioural resilience was related to NPY, as stress exposure decreased NPY expression in the hippocampus, an effect that was absent in animals with treadmill exercise (118).

Finally, NPY was suggested to be a protective factor in the stress-induced memory impairment on the radial maze memory task (119). Rats subjected to chronic immobilization stress performed significantly worse during the memory test, an effect associated with enhanced NPY expression in the ARC. Detailed analysis revealed that rats with little or no stress-induced memory impairment (i.e., stress-resilient individuals) had the highest NPY levels in the ARC and habenula. It thus seems that stress-induced NPY expression is blunted in susceptible individuals, indicating a maladaptive stress response system (119).

6 Role of NPY in stress resilience: evidence from human studies

Stress resilience in humans has often been addressed in connection with the study of PTSD patients. In the aftermath of trauma these patients re-experience the traumatic event (distressing memories or dreams), develop strategies to avoid confrontation with the trauma (avoidance of conversations about the incident, avoidance of places associated with the trauma) and show symptoms of increased arousal such as sleep disturbances (120). Interestingly, PTSD develops only in a subpopulation of trauma-exposed subjects, while the majority stays healthy. It appears as if individual coping strategies determine how humans react to extreme stressful situations. The stress-resilient individuals seem to be protected by genetic, molecular and/or environmental factors (e.g., family, social contacts) preventing the development of disease (Figure 1).

Already 15 years ago the anxiolytic properties of NPY in rodent studies sparked interest in investigating the role of this peptide in PTSD patients. Rasmusson et al. (121) found that basal and yohimbine-stimulated plasma levels of NPY are lowered in PTSD subjects. The effect of yohimbine, an α_2 adrenoceptor antagonist, to raise circulating NPY arises from its ability to increase sympathetic activity due to its presynaptic site of action. Moreover, the baseline NPY levels correlated negatively with combat exposure scale scores and panic (121). Reduced baseline plasma levels of NPY were also found in combat-exposed individuals with PTSD in another study (122). However, the authors noted that NPY levels were diminished also in combat-exposed individuals without PTSD, indicating that trauma itself is the major factor for plasma NPY regulation. In contrast, motor vehicle accident survivors with depression or PTSD do not present with alterations in serum NPY levels,

which is at variance with the afore-mentioned hypothesis (123). A further study investigating combat-related PTSD came up with an opposite result, with plasma NPY levels in combat-exposed veterans without PTSD being higher than in non-exposed veterans (124). Interestingly, a subanalysis of combat-exposed veterans without PTSD revealed that those with a history of past PTSD had the highest NPY levels, suggesting that the ability to overcome trauma-induced disease (i.e. developing resilience) is related to high levels of NPY expression.

As concerns were raised whether plasma NPY accurately reflects NPY levels in the CNS (125), other studies focused on NPY levels in the cerebrospinal fluid (CSF). A study employing this approach showed that combat-exposed veterans with PTSD have lower CSF NPY levels than healthy men (126). Furthermore, a recent report from the same group showed that combat-exposed veterans with PTSD have lower CSF NPY than combat-exposed veterans without PTSD (127). This is in line with the above-mentioned rodent studies suggesting that high cerebral levels of NPY represent an important resilience factor for stress-induced disturbances, while low NPY levels promote behavioural disruption (116,117). It appears as if high NPY concentrations in the CSF can prevent the development of trauma-induced PTSD.

The stress resilience-promoting properties of NPY were also investigated in relation to psychological hardiness, a personality trait that refers to the three interrelated personality characteristics known as commitment, control and challenge (128). Together these personality characteristics appear to protect individuals from the negative health effects of stress. In a cohort of Norwegian navy cadets with overall high psychological hardiness scores it was found that “unbalanced” hardiness subjects (with low scores in the challenge parameter) had lower blood NPY levels in the context of a highly stressful military exercise than “balanced” individuals, which points to an impaired ability to cope with the stressful situation (128). Furthermore, the balanced hardiness group showed a more pronounced NPY rise in the face of stress, indicating a more adaptive stress response. Another study investigated ways to improve stress resilience in relation to NPY (129). Specifically, marines completing a mindfulness-based mind fitness training (an 8-week series of psychological instructions and individual practices with the aim to enhance stress resilience) had lower plasma NPY levels after a stressful military exercise than soldiers without a similar training. The authors explain the beneficial effect of this training scheme by an improvement in the efficient use of neural processing resources and thus an altered autonomic response to stress (129).

A role of NPY as a stress resilience factor in humans is also supported by genetic evidence. Analysis of various single nucleotide polymorphisms (SNPs) of the NPY gene revealed NPY genotype-dependent alterations in the central processing of stress or emotional events. Accordingly, individuals with a low-expression NPY genotype show exaggerated amygdala reactivity to threat-related facial expressions, which may reflect an overreaction to a stressful event (130). Similarly, the rostral anterior cingulate cortex is activated in low-expression NPY genotypes when reading negatively valenced words, while high-expression NPY genotype individuals show the opposite reaction (131). Furthermore, individuals with a low-expression NPY genotype experience enhanced negative affect before and after a pain

stimulus. It thus appears that a low-expression NPY genotype predisposes individuals to hyper-responsiveness to negative stimuli and potentially to subsequent disease development (131). In line with these findings, carriers of the C allele of the NPY SNP rs16147 present with increased bilateral amygdala activation while viewing angry faces and a significant association with depression and anxiety when exposed to early life psychological adversity (132,133). Other studies found that variation of the NPY gene confers disease risk in the context of extreme stress. For instance, the NPY rs16147 SNP increases the likelihood to develop a generalized anxiety disorder after hurricane exposure (134). Individuals with high hurricane exposure and the “TT” genotype of the SNP were 3.6 times more at risk for being diagnosed with the disorder. Furthermore, in another report, carriers of the same SNP displayed HPA axis dysregulation in response to a psychological stress task dependent on early life adversity (135). Likewise, the risk for anxiety susceptibility after childhood adversities depends on the NPY genotype, with three SNPs of the NPY gene (rs16142, rs2023890, and rs17374047) increasing the risk (136). The relevance of NPY as a stress resilience factor has been confirmed in a study with monkeys. Macaques exposed to early life adversity exhibit enhanced arousal during stress and lowered CSF levels of NPY when carrying a SNP in the NPY promoter region (137).

7 NPY as a potential therapeutic for PTSD

Treatment of human primary psychiatric diseases with neuropeptide therapeutics such as NPY is challenging as it faces several technical limitations. To date these include systemic route of administration, short *in vivo* stability, poor BBB penetration as well as complexity and costs of manufacture (138). Particularly the inability of neuropeptides to pass the BBB and the disadvantages of oral or systemic administration (absorption, first-pass metabolism, plasma protein binding, time to reach the brain, peripheral and central side effects) slowed the progress in the development of neuropeptide therapeutics (139). Meanwhile research has focused on a promising non-invasive way to circumvent problems associated with systemic neuropeptide administration, namely intranasal drug delivery. This administration route has been shown to achieve direct CNS delivery of various compounds with rapid increases in CNS levels and, in parallel, to avoid drawbacks of peripheral drug treatment (139).

NPY application via the intranasal administration route has been repeatedly shown to exert beneficial behavioural effects. After exposure to single prolonged stress (SPS), a rat model of PTSD, Serova et al. (140) observed a reduction of anxiety and depression-like behaviour in animals receiving a single pre-stress dose of intranasal NPY. Furthermore, intranasal NPY reduced the perceived severity of stress and prevented stress-induced dysregulation of the HPA axis and noradrenergic activity (140). In a therapeutic study design, NPY was able to ameliorate the SPS-induced behavioural disturbances when administered immediately or even 7 days after stress exposure (140–142). Similarly to pre-stress NPY administration, post-stress intranasal NPY application also prevented HPA axis dysregulation (143).

In humans evidence for a therapeutic effect of intranasal NPY is limited. A small pilot study found that intranasal NPY application is associated with very low systemic absorption rates, inducing local vasoconstriction but failing to modify mean arterial pressure or heart rate, which indicates a good safety profile (144). The ability of NPY to influence CNS function

when applied via the nasal route was inferred from an investigation of central mechanisms of food intake. Specifically, intranasal NPY attenuated electrocortical signs of meal-related satiety (145). To our knowledge there is no published study on the effects of NPY or NPY analogues on neuropsychiatric disease in humans. However, the potential of intranasal NPY administration as a treatment option for PTSD is currently under investigation in a Phase I trial (clinicaltrials.gov).

8 Role of NPY in neurodegenerative diseases

Neurodegenerative diseases represent a leading health issue and comprise wide-spread pathologies such as Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD). Genetic, environmental as well as toxic factors contribute to the pathogenesis of these neurodegenerative diseases to a differential degree. Stress, on the one hand, may trigger or exacerbate the disease course while the disease symptoms, on the other hand, are a source of stress to the patients (146,147). NPY has been implicated in all of these disorders either as a biomarker, a neuroprotective factor or a potential therapeutic.

NPY and Alzheimer's disease

Reductions of NPY levels in plasma, CSF and brain of AD patients sparked interest in the relation of this neuropeptide with AD (148,149). Soon afterwards a negative correlation between NPY levels in the CSF and duration of the disease was described (150). In parallel it was found that cortical NPY neurons are severely damaged during AD (151). The use of transgenic AD mouse models confirmed that especially cortical but also hippocampal neurons expressing NPY are strongly affected by the AD pathology, which points to a particular vulnerability of these neurons and a role of NPY in AD pathophysiology (152–154). Importantly, hippocampal NPY neurons are affected already in the early stages of AD. NPY may thus constitute a potential biomarker of treatment efficacy during AD drug development (152).

Additionally, several reports attest to the therapeutic efficacy of NPY in various experimental AD models. Infusion of NPY C-terminal fragments into the brains of APP (amyloid precursor protein) transgenic mice ameliorates neurodegenerative pathology, and pretreatment of cultured primary human neurons with NPY fragments prevents the cytotoxic effects of beta-amyloid$_{(1-42)}$ (Aß$_{(1-42)}$) (155). A number of in vitro experiments also suggests a neuroprotective effect of NPY. For instance, the toxic effect of Aß$_{(25-35)}$ on SH-SY5Y neuroblastoma cell viability is prevented by a 24 h pretreatment with NPY (156). In a similar setting involving primary cortical neurons of rats, NPY is likewise able to prevent the deleterious effects of Aß$_{(25-35)}$ (157). The neuroprotective effect of NPY in these studies is associated with changes in nerve growth factor and brain-derived neurotrophic factor gene expression (156–159).

In-vivo experiments show that NPY plays a role in the behavioural changes associated with AD pathology. In the colchicine-induced rat model of AD, memory impairments in the Morris Water Maze are ameliorated by NPY and the Y1 receptor agonist [Leu^{31},Pro^{34}]-NPY, whereas the Y1 receptor antagonist BIBP3226 produces the opposite effect (160). While this study suggests that the Y1 receptor is crucial in the AD-related cognitive

impairment, beneficial effects of NPY may also be mediated by Y2/Y5 receptors which are able to prevent excitotoxicity by inhibiting glutamate release (161). In line with this finding, NPY prevents Aß$_{(1-42)}$-induced depression-like behaviour and spatial memory impairments in mice, but fails to do so after pretreatment with BIIE0246, a Y2 receptor antagonist (162).

In contradiction of these findings there are also reports that question the involvement of NPY in the AD disease course. For instance, a human study investigating NPY single nucleotide polymorphisms did not find an association with increased AD risk (163), and plasma levels of NPY were found unaltered in a more recent study of AD patients (164)These findings do not necessarily negate an involvement of cerebral NPY in the AD pathology, which needs to be proven by clinical trials of pharmacological interventions in the NPY system.

NPY and Huntington's disease

In contrast to AD which causes a reduction of NPY-expressing cells, the number of NPY-expressing cells in HD is increased in the basal ganglia, cortex and the subventricular zone (165–167). It thus appears as if NPY-containing interneurons are spared from the degenerative process, which in the striatum affects primarily medium-sized spiny projection neurons expressing GABA (168), and the increase in the number of cerebral NPY neurons reflects an attempt to balance the loss of other neurons. The enhanced NPY levels in the subventricular zone may be of further clinical significance, given that the cell proliferation rate in this region, one of the few brain areas capable of adult neurogenesis, correlates with HD disease severity (169). The HD-related enhanced neurogenesis is likely to be a counterregulatory mechanism to compensate for the progressive neuronal cell loss during the disease course. NPY is known to increase neurogenesis (170), and a further increase in cerebral NPY expression by pharmacological interventions may be a promising treatment strategy in HD. In fact, NPY has already been shown to be of therapeutic value in mice with HD pathology. Specifically, icv NPY administration increases survival time and ameliorates motor performance as well as cerebral atrophy of R6/2 mice (171). A recent human study disclosed a modest association of HD onset age with two NPY promoter variations and a strong association with a Y2 receptor single nucleotide polymorphism (172). Patients with the high expression Y2 receptor genotype had a later age of disease onset. In addition, NPY and the Y2 receptor agonist NPY$_{(3-36)}$ were found to protect PC12 cells expressing mutant huntingtin (htt) exon 1 against mutant htt-induced cell death (172).

NPY and Parkinson's disease

An association of NPY with PD is supported by findings that disruption of the nigrostriatal pathway by 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine results in an increased number of striatal NPY-expressing neurons (173–175). In line with this finding, post-mortem analysis of brain tissue from PD patients reveals an increase of NPY-expressing neurons in the striatum (176), which may be related to the loss of dopaminergic tone on the striatal NPY interneurons. Interestingly, NPY levels in the CSF of PD patients appear to be lower than in healthy individuals (177), which may point to a reduction of NPY release or increased NPY turnover. A recent study suggests that NPY exerts a neuroprotective action in both in-vivo and in-vitro models of PD (178). In vitro,

NPY protects SH-SY5Y dopaminergic neuroblastoma cells from 6-OHDA-induced toxicity, while in vivo NPY preserves the nigrostriatal dopaminergic pathway from neurodegeneration. These neuroprotective effects are blocked by BIIE0246, a Y2 receptor antagonist, which suggests that the NPY effects are mediated via this receptor. Besides its potential therapeutic effect, NPY has also been implicated in the weight gain associated with deep brain stimulation of the subthalamic nucleus, a current treatment option of PD. Two studies found increased circulating NPY levels as a potential factor relevant to this side effect (179,180).

9 Conclusions

Since its discovery and isolation from porcine brain extracts, NPY has gained significant attention for its anti-stress and anxiolytic properties. Exciting new lines of research implicate the peptide as an important mediator of stress resilience, the ability to cope with stress, and as a neuroprotective factor in neurodegenerative diseases. These implications are supported by genetic, molecular and pharmacological studies. Extensive analysis identifies the amygdala-hippocampus network and associated limbic brain areas as key components in NPY-mediated stress resilience. While several animal models demonstrate the therapeutic efficacy of NPY in the context of neuropsychiatric and neurodegenerative disease, data from human studies are still inconclusive. Due to the unfavourable kinetics of neuropeptide drugs there is a need for novel therapeutic strategies that enable neuropeptide therapeutics to bypass or cross the BBB. Following this approach, intranasal NPY represents a promising strategy for the treatment of PTSD.

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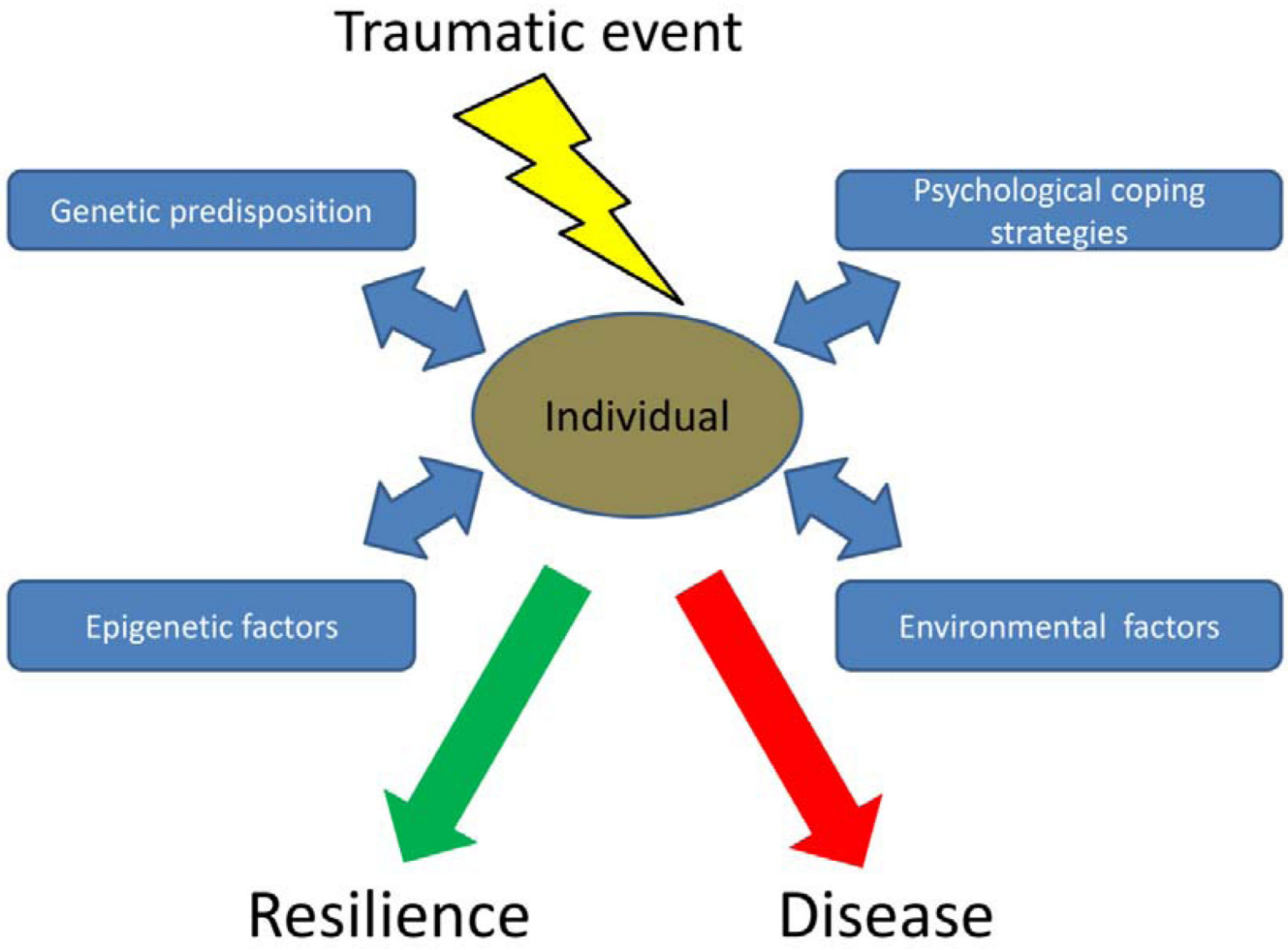

Figure 1. Key factors for the individual response to an extreme traumatic event.

Various genetic, epigenetic, psychological and environmental susceptibility and/or resilience factors determine whether individuals develop disease or stay healthy (resilience).

Table 1:

Stress-induced effects on NPY gene expression in selected brain areas.

Brain region	Type of stress	Effect on NPY gene expression	Species	Ref
Amy	60-min restraint stress	↓ 1+2h post-stress	Sprague-Dawley rats	(34)
	60-min restraint stress (10 days)	↑ 2h post-stress	Sprague-Dawley rats	(35)
	60-min water avoidance stress (7 days)	↓ 1d post-stress	C57BL/6N mice	(38)
	30-min water avoidance stress	No effect	C57BL/6N mice	(33)
BLA	15-min footshock stress	↑ 2w post-stress	Wistar rats	(32)
	12 trials in Morris Water Maze	↓ 5h post-stress	Sprague-Dawley rats	(37)
MeA	60-min restraint stress (1,3 or 10 days)	↑ 0min post-stress (after 3 sessions)	Wistar-Kyoto rats	(36)
HT	60-min restraint stress	No effect	Sprague-Dawley rats	(34)
	60-min restraint stress (10 days)	No effect	Sprague-Dawley rats	(35)
	60-min water avoidance stress (7 days)	No effect	C57BL/6N mice	(38)
	30-min water avoidance stress	↑ 0min post-stress	C57BL/6N mice	(33)
	30-min restraint stress	↑ 4h post-stress	CD1 mice	(41)
	60-min immobilization stress	↑ 0h, 24h + 48h post-stress	Wistar rats	(42)
ARC	60-min restraint stress	↑ 24h post-stress	Sprague-Dawley rats	(39)
	60-min restraint stress (1,3 or 10 days)	↑ 0min post-stress (after 1 or 3 sessions)	Wistar-Kyoto rats	(36)
	15-min footshock stress	↑ 2h post-stress	Wistar Utrecht:Wistar Unileve rats	(40)
	Air puff (1 or 10 days)	No effect	Wistar-Kyoto rats	(43)
Hip	30-min water avoidance stress	No effect	C57BL/6N mice	(33)
	60-min water avoidance stress (7 days)	No effect	C57BL/6N mice	(38)
	60-min restraint stress (1,3 or 10 days)	↓ 0min post-stress (after 10 sessions)	Wistar-Kyoto rats	(36)
DG	60-min restraint stress	↑ 6h post-stress	Sprague-Dawley rats	(39)
	12 trials in Morris Water Maze	↑ 5h post-stress	Sprague-Dawley rats	(37)
LC	15-min footshock stress	↓ 2w post-stress	Wistar rats	(32)
	60-min restraint stress (1,3 or 10 days)	No effect	Wistar-Kyoto rats	(36)
	Air puff (1 or 10 days)	↑ 30min post-stress (after 10 days)	Wistar-Kyoto rats	(43)

↑ or ↓ denote increased or decreased NPY mRNA levels at the given time point after stress exposure; Amy, amygdala; ARC, arcuate nucleus; BLA, basolateral amygdala; DG, dentate gyrus; Hip, hippocampus; HT, hypothalamus; LC, locus coeruleus; MeA, medial amygdala