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PYY_{3-36}: Beyond food intake

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Abstract

The gastrointestinal hormone peptide tyrosine tyrosine 3-36 (PYY_{3-36}) has attained broad recognition with respect to its involvement in energy homeostasis and the control of food intake. It is mainly secreted by distal intestinal enteroendocrine L-cells in response to eating and exerts both neurally mediated paracrine and endocrine effects on various target organs. In addition to its gastrointestinal effects, PYY_{3-36} has long been known to inhibit food intake. Recent closer examination of the effects of PYY_{3-36} revealed that this gut-derived peptide also influences a wide spectrum of behavioral and cognitive functions that are pivotal for basic processes of perception and judgment, including central information processing, salience learning, working memory, and behavioral responding to novelty. Here, we review the effects of PYY_{3-36} that go beyond food intake and provide a conceptual framework suggesting that several apparently unrelated behavioral actions of PYY_{3-36} may actually reflect different manifestations of modulating the central dopamine system.

Key words: Dopamine; energy homeostasis; eating; incentive salience; gut peptide.

1. Introduction

Peptide tyrosine tyrosine (PYY) is a peptide hormone which, together with pancreatic polypeptide (PP) and neuropeptide Y (NPY), comprises the PP family of peptides (Berglund et al., 2003). The two existing forms of PYY differ by two amino acids (Grandt et al., 1994; Medeiros and Turner, 1994). PYY_{1-36} is released from enteroendocrine L-cells in response to nutrient signals in the chyme. In the blood, PYY_{1-36} is rapidly converted to PYY_{3-36} by the ubiquitously expressed enzyme, dipeptidyl-peptidase IV (DPP-IV), which cleaves the two N-terminal amino acids (Mentlein et al., 1993). Hence, PYY_{3-36} is the major circulating form of the peptide, known to exert different and sometimes opposite biological functions than PYY_{1-36} (Grandt et al., 1994) (**Figure 1**).

As extensively reviewed elsewhere (Karra and Batterham, 2010; Schwartz and Holst, 2010; Walther et al., 2011), the distinct biological functions exerted by PYY_{1-36} and PYY_{3-36} have been explained by their different binding affinities for the five Y receptor subtypes in mammals, Y1, Y2, Y4, Y5 and Y6. All are inhibitory G-protein coupled receptors that reduce cyclic-AMP and the mobilization of intracellular calcium (Michel et al., 1998; Berglund et al., 2003). Whereas PYY_{1-36} has similar affinities for the Y1 and Y2 receptor, PYY_{3-36} is a high-affinity Y2 receptor ligand (Walther et al., 2011). In the periphery, the Y2 receptor is expressed by parasympathetic and sympathetic sensory neurons, in addition to intestinal and some vascular cells (Widdowson, 1993; Gehlert, 1994; Cabrele and Beck-Sickinger, 2000). The Y2 receptor is also abundantly expressed in several regions of the central nervous system (CNS), including limbic and cortical areas (Stanic et al., 2006; Walther et al., 2011). In neuronal tissue, the Y2 receptor is localized mainly presynaptically, inhibiting neurotransmitter release upon activation (Smith-White et al., 2001; Stanic et al., 2011). Such autoreceptor functions of the Y2 receptor are well documented, for example with regard to NPY release in hypothalamic

areas, where Y2 receptor agonists including PYY_{3-36} inhibit NPY synthesis and secretion (King et al, 1999; Smith-White et al, 2001; Batterham et al, 2002; Challis et al, 2003).

PYY is secreted by mainly distal intestinal enteroendocrine L-cells in response to eating, and plasma levels of PYY_{3-36} remain elevated for several hours after meals (Adrian et al., 1985; Stanley et al., 2004). The best known functions of PYY_{3-36} are in the gastrointestinal system where it regulates secretions (Yang, 2002) and motility (Immamura, 2002). Many of its actions contribute to the 'ileal brake,' whereby secretions of the distal small intestine slow gastric emptying when nutrients reach the ileum.

More recently, PYY_{3-36} has attained broad recognition with respect to its involvement in energy homeostasis and the control of food intake (see Manning and Batterham, 2014). A landmark study by Batterham et al. (2002) directly implicated PYY_{3-36} in the physiological inhibition of food intake. This effect is mediated through the Y2 receptor (Batterham et al., 2002) and has been documented in diverse conditions and several species, including rodents and humans (**Table 1**). Basal levels are lower and the meal-induced release of PYY_{3-36} is blunted in obese individuals (Alvazrez Bartolomé et al., 2002; Batterham et al., 2003; le Roux et al., 2006; Guo et al., Sodowski et al., 2007). Also, PYY overexpression protects against diet-induced obesity (Boey et al., 2008). Importantly, PYY_{3-36} administration reduces food intake similarly in obese and non-obese subjects (Batterham et al., 2003; Sloth et al., 2007), implying that obesity does not decrease PYY_{3-36} sensitivity. Collectively, these observations have attracted considerable interest in PYY_{3-36} as a potential pharmacotherapy for obesity (Karra et al., 2009).

While the precise physiological mechanisms whereby PYY_{3-36} inhibits eating remain unclear, it effectively crosses the blood-brain-barrier from the plasma (Nonaka et al., 2003) and acts centrally as a relatively selective Y2 receptor agonist (Grandt et al.,

1994). Y2 receptor expression is abundant on hypothalamic arcuate neurons that co-express NPY and agouti-related peptide (AgrP) (Broberger et al., 1997; Hahn et al., 1998), and administration of PYY_{3-36} directly into the Arc reduces food intake (Batterham, 2002). Consistent with its action as an inhibitory presynaptic receptor, one prevalent hypothesis suggests that activation of the Y2 receptor inhibits arcuate NPY neurons and reduces the NPY-mediated inhibition of neighboring anorexigenic neurons co-expressing pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) (Broberger et al., 1997; Morton et al., 2014).

In addition to hypothalamic sites of action, there are also alternative (but not mutually exclusive) mechanisms by which PYY_{3-36} could inhibit food intake, particularly in light of the widespread expression of Y2 receptors in cortical and subcortical brain areas (Stanic et al., 2006, 2011). Hence, in addition to NPY neurons, some γ-aminobutyric acid (GABA) or glutamate neurons also express the Y2 receptor (Stanic et al., 2006, 2011). Y2 agonists such as PYY_{3-36} may thus readily influence neural circuits in diverse brain regions. Consistent with this, using functional magnetic resonance imaging (fMRI), Batterham and colleagues found that peripheral administration of PYY_{3-36} induces neuronal activation in several brain regions, including target areas of the mesolimbic and nigrostriatal dopaminergic pathways, brainstem areas including the nucleus tractus solitarii (NTS), and cortical areas including the orbitofrontal cortex (Batterham et al., 2007). Consistent with these findings, our research group also observed widespread neuronal activation following peripheral PYY_{3-36} administration in rats (Stadlbauer et al., 2013a; for further details, see Section 5).

In view of these neuronal effects, it is reasonable to hypothesize that PYY_{3-36} has functional significance in the brain beyond its role in controlling food intake, and experimental research in rodents has recently begun to explore the effects of PYY_{3-36} on

other behaviors. Here, we summarize some of those findings and provide a conceptual framework suggesting that several apparently unrelated behavioral actions of PYY_{3-36} actually reflect different manifestations of modulating the mesocorticolimbic dopamine system.

2. PYY_{3-36} and sensitivity to psychostimulant drugs

Studies in both humans and rats indicate that the peripheral administration of PYY_{3-36} leads to activation of central dopaminergic pathways (Batterham et al., 2007; Stadlbauer et al., 2013a). The largest populations of dopamine cells are localized in two neighboring midbrain nuclei, namely the ventral tegmental area (VTA; A10 cell group) and the substantia nigra (SN; A9 cell group) (Tzschentke, 2001; Björklund and Dunnett, 2007; Van den Heuvel and Pasterkamp, 2008). The majority of VTA dopamine cells projects to limbic and cortical areas along the mesolimbic and mesocortical dopamine pathways, respectively, whereas a large part of the nigral A9 dopamine cells innervate the dorsal striatum forming the nigrostriatal dopaminergic pathway (**Figure 2**). Midbrain dopamine cells are also found in the A8 cell group, which forms a dorsal and caudal extension of the A9 cell group and contains cells that project to both striatal, limbic and cortical areas (**Figure 2**). A8 cells are thus an integral part of the mesolimbic, mesocortical, and nigrostriatal dopamine pathways (Björklund and Dunnett, 2007; Roeper, 2013).

Among other functions, the mesolimbic dopaminergic pathway is important in mediating the behavioral and locomotor responses to drugs of abuse (Soderpalm and Ericson, 2013), whereas the nigrostriatal pathway is critically involved in the control of voluntary movement and motor stereotypies (Groenewegen, 2003). Recent neuropharmacological investigations in mice demonstrate that peripheral

administration of PYY_{3-36} markedly modulates these dopamine-related behavioral functions (Stadlbauer et al., 2014). Specifically, pretreatment with PYY_{3-36} potentiates the locomotor responses to subsequent amphetamine (Amph) exposure and increases stereotypical behavioral reactions to systemic apomorphine (Apo) (Stadlbauer et al., 2014). Amph is an indirect dopamine receptor agonist that efficiently stimulates presynaptic dopamine release (Salahpour et al., 2008), and its administration elicits rigorous locomotor activity (Robinson and Becker, 1986). Apo is a preferential dopamine D1/D2 receptor agonist that dose-dependently increases locomotor activity and other stereotyped behaviors in rodents, including repetitive climbing and leaning (Cabib and Puglisi-Allegra, 1985; Bitanihirwe et al., 2010). The mesolimbic and nigrostriatal dopamine pathways are key neuronal components mediating the behavioral responses to Amph and Apo. Early studies concluded that the locomotor-enhancing effects of low doses of systemic Amph result from increased dopamine transmission in the NAc (Creese and Iversen, 1975; Pijnenburg et al., 1976), particularly in its shell sub-region (Heidbreder and Feldon, 1998). More recent studies suggest that enhanced dopamine release more dorsally in the striatum contributes to Amph-induced locomotor hyperactivity as well (Matthews et al., 2013). The expression of stereotyped behaviors has also often been functionally linked to enhanced activation of striatal dopamine receptors, especially in dorsal parts of the striatum (Arnt et al., 1988; Vasse and Protais, 1989; Charntikov et al., 2011). It has recently been found that PYY_{3-36} potentiates the behavioral responses to both Amph and Apo and that it likely involves increased dopaminergic activity in the mesolimbic and/or nigrostriatal pathways (Stadlbauer et al., 2014). Even though this hypothesis lacks direct confirmation, it is consistent with previous ex-vivo studies reporting that exogenous PYY_{3-36} increases the synthesis and release of dopamine in rat striatal slices (Adewale et al., 2005, 2007).

Work in genetically modified mice lacking the Y2 receptor has provided additional support for the hypothesis that signaling through Y2 receptors can exert a direct influence on striatal dopamine release (Zambello et al., 2011). Thus, accumulating evidence suggests that PYY_{3-36} administration induces neuronal (Batterham et al., 2007; Stadlbauer et al., 2013a), behavioral (Stadlbauer et al., 2014), and neurochemical (Adewale et al., 2005, 2007; Zambello et al., 2011) changes reminiscent of a (transient) hyperdopaminergic state.

3. PYY_{3-36} and behavioral responses to novelty

Responding to a novel environment engages the mesolimbic dopamine system (Bardo et al., 1996; Blanchard et al., 2009), and the magnitude of the response predicts the behavioral responses to dopaminergic psychostimulant drugs (Marinelli and White, 2000). Given these associations, it has been hypothesized that PYY_{3-36}, in addition to its effects on potentiating psychostimulant drug sensitivity, would also enhance novelty seeking. In support of this, we observed that peripheral administration of PYY_{3-36} in mice increases novelty seeking in a novel-object exploration task in which mice were allowed to freely explore an unfamiliar object following habituation to the surrounding context (Stadlbauer et al., 2014). These effects were unlikely to be mediated by possible changes in anxiety-like behavior because identical PYY_{3-36} treatment did not affect behavioral indices of innate anxiety (Stadlbauer et al., 2013b, 2014).

More likely is that the enhancement of novel object exploration displayed by PYY_{3-36}-treated animals is related to changes in incentive salience. Incentive salience is a motivational attribute that increases the attractiveness of a given stimulus and promotes approach behavior towards it (Berridge and Robinson, 1998). Research in rats has found a positive correlation between the amount of novelty seeking and incentive

salience attribution to reward-associated cues (Beckmann et al., 2011). Dopaminergic mechanisms in general, and increased accumbal dopaminergic activity in particular, are critical in regulating the perception and processing of salient stimuli (Berridge and Robinson, 1998; Wise, 2004). For example, manipulations increasing and decreasing dopaminergic activity in the NAc, respectively, enhance and reduce exploratory activity toward novel stimuli (Rebec et al., 1997; Peters et al., 2007; Fukushiro and Frussa-Filho, 2011; Laricchiuta et al., 2014). Furthermore, rats with increased novelty-seeking have a greater behavioral sensitivity to the indirect dopamine receptor agonist cocaine (Beckmann et al., 2011). Similar parallels exist following peripheral PYY_{3-36} administration in mice, where PYY_{3-36} elicits a concomitant increase in the behavioral response to novelty and to Amph (Stadlbauer et al., 2014). Thus, the positive correlations among mesolimbic dopamine activity, novelty seeking, and incentive salience (Bardo et al., 1996; Berridge and Robinson, 1998; Blanchard et al., 2009; Beckmann et al., 2011) all suggest that PYY_{3-36}-induced potentiation of novelty seeking likely involves increased incentive salience attribution to the novel stimuli.

The same processes may also explain the recently reported decreases in social approach behavior following peripheral PYY_{3-36} administration in mice (Stadlbauer et al., 2013b). When given the choice between exploring an unfamiliar mouse and a novel inanimate object, mice (like most other rodents) typically prefer spending more time with the live mouse relative to the inanimate object (Moy et al. 2008; Vuillermot et al., 2011). Following PPY_{3-36} treatment, however, the preference is no longer seen, and PYY_{3-36}-treated mice spend more time with the novel object at the expanse of reduced time spent with the live mouse (Stadlbauer et al., 2013b). Consistent with this, genetic ablation or pharmacological inhibition of the Y2 receptor causes an opposite pattern of effects, including increased social approach behavior (Karl et al., 2010; Morales-Medina

et al, 2012). Hence, stimulation or attenuation of Y2 receptor signaling reduces or increases social approach behavior, respectively, and these effects may at least partially involve altered incentive salience attribution to unfamiliar congenic species and novel inanimate objects.

4. PYY_{3-36} and central information processing

Aberrant salience processing is also involved in the disruption of central information processing, especially when the brain is required to discriminate between relevant and irrelevant stimuli (Smith et al., 2006; Winton-Brown et al., 2014). Under such conditions, increased mesolimbic dopamine activity enhances the salience of irrelevant stimuli, and as a consequence the organism often fails to differentiate between relevant and irrelevant information (Kapur, 2003; Smith et al., 2006). The essence of this phenomenon can be captured by a behavioral paradigm known as latent inhibition (LI), a model of associative learning in which non-reinforced pre-exposures to a to-be-conditioned stimulus (CS) retard subsequent conditioning between the same CS and the unconditioned stimulus (US) (Lubow and Moore, 1959; Lubow, 2005). Prevalent neuropsychological theories posit that LI is caused by the development of selective attention away from the pre-exposed stimulus, so that non-reinforced CS pre-exposure diminishes the perceived salience of the CS during conditioning (Mackintosh, 1975; Lubow et al., 1981; for other neuropsychological theories, see Weiner, 2003 and Lubow, 2005). LI is often referred to as a form of "salience learning" (Young et al., 2005; Nelson et al., 2011), and its expression is taken as index of the tendency of an organism to successfully ignore stimuli that historically predict no significant consequences (Weiner, 2003). Aberrant salience attribution to inconsequential stimuli weakens LI, and is indicative of a susceptibility to distraction by irrelevant information.

Similar types of central information processing can also be assessed using behavioral paradigms that do not involve explicit associative learning processes. One widely used example is prepulse inhibition (PPI) of the acoustic startle reflex, which is the reduction of a startle reaction to a startle-eliciting stimulus (pulse) when it is shortly preceded by a weak stimulus (prepulse) (Hoffman and Searle, 1965; Braff et al., 2001). PPI provides an operational measure of sensorimotor gating, in which central gating mechanisms protect the processing of the information contained in the initial prepulse from distraction by the subsequent pulse stimulus (Graham, 1975; Braff et al., 2001). PPI thus serves to filter or gate intrusive sensorimotor information. Disruption of such gating mechanisms can lead to central stimulus overload and associated dysfunctions in allocating the limited neuronal resources to only the most important stimuli encountered in the environment (Swerdlow et al., 2000; Braff et al., 2001).

As extensively reviewed elsewhere (Swerdlow et al, 2000; Braff et al., 2001; Weiner, 2003; Lubow, 2005; Young et al., 2005), experimental manipulations or pathological conditions that result in increased mesolimbic dopamine activity disrupt both LI and PPI. Weakening of PPI and LI can arise from manipulations that directly target the central dopamine system, such as administering Amph or Apo (Swerdlow et al, 2000; Braff et al., 2001; Weiner, 2003; Lubow, 2005; Young et al., 2005). Alternatively, PPI and LI deficiency can also be induced by manipulations that do not primarily target the central dopamine system, but instead lead to down-stream increases in mesolimbic dopamine signaling (Meyer and Feldon, 2009; Peleg-Raibstein et al., 2012). Hence, increased mesolimbic dopamine signaling is a common neurochemical mechanism for the disruption of PPI and LI, regardless of whether the experimental manipulation or pathological condition directly or indirectly affects the mesolimbic dopamine pathways.

We have recently found that that acute peripheral PYY_{3-36} treatment markedly reduces sensorimotor gating in the form of PPI and salience learning in the form of LI (Stadlbauer et al., 2013b). Intriguingly, the dopamine receptor antagonist haloperidol is effective in blocking PYY_{3-36}-induced PPI disruption (Stadlbauer et al., 2013b), implying that the weakening of central information processing by PYY_{3-36} is mediated by increased dopamine signaling. This is consistent with the report that ablation of the Y2 receptor leads to enhanced PPI (Karl et al., 2010). Thus, increased Y2 activity reduces sensorimotor gating, likely via increasing dopaminergic activity in mesolimbic pathways.

Whether or not PYY_{3-36}-induced attenuation of LI is similarly dependent on dopaminergic mechanisms awaits examination. PYY_{3-36}-induced loss of LI, however, was found to arise from selective effects in the subgroup of animals that had been pre-exposed to the CS before conditioning (Stadlbauer et al., 2013b), suggesting that exogenous PPY_{3-36} is able to abolish the efficacy of repeated CS pre-exposures to reduce the expression of the conditioned response. As a consequence, pre-exposed animals treated with PYY_{3-36} no longer display the typical reduction in the conditioned response as seen in non-treated pre-exposed animals (Stadlbauer et al., 2013b). An important implication is that the PYY_{3-36}-induced disruption of LI does not simply reflect a general deficit in classical conditioning per se, but rather readily mirrors deficits in salience learning that normally regulate the expression of LI (Weiner, 2003; Lubow, 2005; Young et al., 2005; Nelson et al., 2011). While still hypothetical, these findings are compatible with a neuropsychological model, in which PYY_{3-36} can enhance the salience of irrelevant stimuli through neurochemical processes involving increased mesolimbic dopaminergic activity (Kapur, 2003; Smith et al., 2006).

5. PYY_{3-36} and cognition

Signaling at the Y2 receptor has been further implicated in certain types of learning and memory (Borbély et al., 2013), with most data suggesting that activation of the Y2 receptor has beneficial effects on long-term memory. For example, Redrobe et al. (2004) found that mice lacking the Y2 receptor have a selective impairment in long-term retention of spatial memory and long-term memory for objects. Similar effects were observed following acute pharmacological blockade of the Y2 receptor in mice (dos Santos et al, 2013). Y2 receptor signaling has also been implicated in short-term memory, but in contrast to its detrimental effects on long-term memory, attenuation of Y2 signaling exerts beneficial effects on short-term memory (Gonçalves et al., 2012). This "double-edged sword" effect of facilitating long-term memory but impeding short-term memory is consistent with a dual-process model of memory, in which short-term and long-term memory are separate and sometimes competing processes (Sanderson et al., 2009; Sanderson and Bannerman, 2012).

When we directly examined the effects of PYY_{3-36} on learning and memory, we found that intraperitoneal PYY_{3-36} administration markedly impaired working memory in mice (Stadlbauer et al., 2013b). Working memory refers to a short-term memory buffer used to hold relevant information temporarily active in order to guide on-going behavior (Baddeley, 2003). Hence, the negative influence of PPY_{3-36} on working memory is consistent with the concept that activation of Y2 receptor signaling impedes short-term forms of memory (Gonçalves et al., 2012).

Successful performance in working memory tests depends on several factors. First, the test subject must allocate appropriate attention to the relevant stimuli, both during the initial acquisition (learning) trial and subsequent expression (memory) trials. Second, the subject must retrieve the relevant short-term information based on its

previous action during the acquisition pause in order to effectively complete the task on a subsequent memory trial. This cognitive demand is further dependent on the amount of experienced proactive interference, which occurs when cognitive processing during (multiple) acquisition trials negatively affects performance on subsequent test trials (Hartshorne, 2008). Hence, there are several potential neurocognitive mechanisms by which PYY_{3-36} could disrupt working memory. In view of the marked effects of PYY_{3-36} on salience processing and selective attention (see Section 4), it seems feasible that attentional deficits are involved. This interpretation would also be consistent with recent reports that working memory performance positively correlates with central information processing capacity (Singer et al., 2013), both of which are reduced by peripheral PYY_{3-36} administration in mice (Stadlbauer et al., 2013b).

6. Modulation of GABA-dopamine interactions by PYY_{3-36}: A common pathway for diverse behavioral changes?

As detailed above, studies from PPY_{3-36}-treated mice (Stadlbauer et al., 2013b, 2014), complemented by studies using Y2 receptor-deficient mice or preferential Y2 receptor antagonists (Redrobe et al., 2004; Karl et al., 2010; Zambello et al., 2011; Gonçalves et al., 2012; Morales-Medina et al, 2012), document that PYY_{3-36} modulates behavioral and cognitive activities in addition to simply reducing food intake. An important question is whether the diverse repertoire of neurobehavioral and neurocognitive changes involves different neuronal and neurochemical processes, or whether it can be explained by a common neuronal mechanism.

In support of the latter, many of the behavioral functions influenced by PYY_{3-36} are critically regulated by subcortical dopamine activity. These include Amph-induced locomotor hyperactivity (Robinson and Becker, 1986; Heidbreder and Feldon, 1998),

Apo-induced behavioral stereotypies (Arnt et al., 1988; Vasse and Protais, 1989; Charntikov et al., 2011), novelty seeking (Bardo et al., 1996; Berridge and Robinson, 1998; Blanchard et al., 2009), sensorimotor gating (Swerdlow et al., 2000, 2001; Braff et al., 2001), and selective attention and salience learning (Weiner, 2003; Young et al., 2005), all of which are changed by peripheral PYY_{3-36} administration (Stadlbauer et al., 2013b; 2014). Hence, the central pro-dopaminergic effects of PYY_{3-36} may provide a common mechanism underlying the induction of different behavioral alterations. This interpretation fits with the general proposition that a core disruption in a key neurotransmitter system can give rise to diverse behavioral and cognitive alterations (Meyer and Feldon, 2009, 2010). Consistent with this, many clinical behavioral disorders involve abnormally enhanced dopamine activity (Kapur, 2003; Winton-Brown et al., 2014).

Given the importance of dopamine for so many behaviors, and the observation that PYY_{3-36} influences dopamine functioning, the determination of how PYY_{3-36} influences dopamine signaling is an important goal. Available data suggest that PYY_{3-36} increases striatal dopamine release via a presynaptic modulation of dopamine release in target areas rather than from a direct action on midbrain dopamine cell activity per se (**Figure 3**). Double immunoenzyme staining of the neuronal early gene product c-Fos and the dopaminergic marker tyrosine hydroxylase (TH) revealed that peripheral PYY_{3-36} treatment does not activate TH-positive dopamine cells in the VTA or SNc (Stadlbauer et al., 2014). It does, however, induce neuronal activation in ventral (NAc) and dorsal (CPu) parts of the striatum (Stadlbauer et al., 2014), which are the two primary areas innervated by VTA and SNc dopaminergic neurons (Van den Heuvel and Pasterkamp, 2008). Hence, striatal neuronal activation following PYY_{3-36} treatment can emerge in the absence of direct activation of the mesoaccumbal (VTA to NAc) or nigrostriatal (SNc to

CPu) dopaminergic pathways. Consistent with this, ex-vivo pharmacological studies in rat brain striatal slices demonstrated that PYY_{3-36} increases dopamine release even though the dopaminergic axon terminals were disconnected from their cell bodies (Adewale et al., 2007).

Y2 receptors are localized presynaptically where they inhibit neurotransmitter release (Smith-White et al., 2001; Stanic et al., 2006). This has been well documented for hypothalamic NPY release, where Y2 agonists including PYY_{3-36} inhibit NPY synthesis and secretion (King et al, 1999; Smith-White et al, 2001; Batterham et al, 2002; Challis et al, 2003). The Y2 receptor is also abundantly expressed in the striatum and many other subcortical structures (Stanic et al., 2006). Interestingly, however, this expression seems to be restricted to non-dopaminergic cells and fibers, as presynaptic dopaminergic terminals lack a clear expression of Y2 receptors (Stanic et al., 2011). The implication is that any modulation of striatal dopamine release by PYY_{3-36} is unlikely to involve direct Y2 signaling at dopaminergic fibers. Instead, it may be largely driven by other neurotransmitter systems that are functionally connected to presynaptic dopamine terminals. In particular, PYY_{3-36} may activate Y2 receptors expressed on striatal GABAergic interneurons, which in turn can robustly attenuate striatal dopamine release by providing inhibitory inputs to presynaptic dopamine terminals (Smith and Kieval, 2000; David et al., 2005). Since activation of Y2 receptors induces neuronal inhibition, it can be expected that PYY_{3-36}-induced activation of these receptors inhibits neuronal activity of striatal GABAergic interneurons (Acuna-Goycolea et al., 2005; see also **Figure 3**). Such inhibition would, in turn, weaken the inhibitory inputs of striatal GABAergic interneurons onto presynaptic dopamine terminals, thereby facilitating the release of dopamine (**Figure 3**). Hence, PYY_{3-36} may induce its pro-dopaminergic effects by

weakening the fast-forward inhibition of presynaptic dopaminergic fibers by striatal GABAergic interneurons.

Consistent with this, both human imaging studies (Batterham et al., 2007) and immunohistochemical findings in mice (Stadlbauer et al., 2014) indicate that PYY_{3-36} induces neuronal activation in striatal areas, and leads to increased neuronal activity in down-stream brain areas that are directly innervated by striatal neurons, including the ventral palladium (VP) (Stadlbauer et al., 2014). The VP is a primary projection site of the ventral striatum (Groenewegen et al., 1996; Groenewegen, 2003) and has been implicated in behavioral functions that are affected by exogenous PYY_{3-36} treatment, including sensorimotor gating (Kodsi and Swerdlow, 1995; Kretschmer and Koch, 1998), behavioral sensitivity to dopamine-stimulating drugs such as Amph (Swerdlow and Koob, 1987; Mele et al., 1998), and incentive salience attribution (Tindell et al., 2005). The general consensus is that these behavioral and neuropsychological functions are markedly affected by increased VP activity similarly to what has been observed following peripheral PYY_{3-36} administration (Stadlbauer et al., 2013b, 2014).

It is likely that PYY_{3-36}-induced suppression of GABAergic activity is not restricted to striatal areas (Acuna-Goycolea et al., 2005), which in turn may have functional relevance as well. For example, working memory is dependent on the integrity of GABAergic signaling, especially in cortical structures such as the PFC (Lewis et al., 2005; Lewis and Moghaddam, 2006). GABA-mediated inhibition is an essential component in the synchronization of neuronal rhythms and oscillatory activity (Lewis et al., 2005; Kohl and Paulsen, 2010), and these in turn are important for working memory (Lewis et al., 2005; Lewis and Moghaddam, 2006). According to the prevailing view, reduced activity of cortical GABAergic interneurons leads to reduced peri-somatic inhibition of excitatory pyramidal cells, and consequently impairs the synchronized excitatory neural response

that is required for optimal working memory functions (Lewis et al., 2005; Lewis and Moghaddam, 2006; Kohl and Paulsen, 2010). It is unknown whether and/or to what extent PYY_{3-36} could interfere with such neuronal synchronization processes. Given that PYY_{3-36} can efficiently reduce GABAergic activity (Acuna-Goycolea et al., 2005), however, interference with GABA-mediated neuronal synchronization may offer a plausible mechanism by which PYY_{3-36} disrupts working memory (Stadlbauer et al., 2013b).

7. Effects of PYY_{3-36} on food intake and other behaviors: Separate functional entities or pieces of the same puzzle?

Activation of the Y2 receptor by $PYY_{3–36}$ has thus far mostly been studied with respect to the control of food intake and regulation of energy homeostasis (Chandarana and Batterham, 2008; Neary and Batterham, 2009). Although some of these studies also looked at brain areas involved in the hedonic control of eating (e.g., Batterham et al., 2007), most of them focused on $PYY_{3–36}$'s effect on homeostatic brain regions such as the hypothalamus (Broberger et al., 1997; Hahn et al., 1998). As summarized in the preceding sections, however, there is increasing evidence that PYY_{3-36} modulates numerous other behavioral and cognitive functions beyond eating and activates a broad spectrum of brain regions and neurotransmitter systems. This raises the intriguing question as to whether the effects of PYY_{3-36} on food intake and other behaviors represent distinct and independent behavioral processes, or whether they may be somehow interrelated.

Current knowledge does not readily allow for an evidence-based answer to this question. There are, however, a number of potential neural and neuropsychological processes that could provide a link between the PYY_{3-36}-induced inhibition of food intake and other functional changes in seemingly distinct behavioral domains. One

possible link relates to the role of dopamine in reward and incentive values on the one hand, and to the associations between reward and eating behavior on the other hand (Hnaskoa et al., 2004). These functional associations are highly complex and likely involve intricate interactions among homeostatic, hedonic, motivational, and associative processes (Berthoud et al., 2011; Glimcher, 2011; Kenny, 2011; Salamone and Correa, 2012; Richard et al., 2013; Morton et al., 2014). As part of these interactions, it is becoming increasingly evident that dopamine signaling cannot simply be equated with hedonic experience, i.e., the feeling of pleasure. Indeed, many studies cast doubt on the "common dopamine hypothesis of reward" concept, which in essence suggests that the experience of pleasure positively correlates with mesolimbic dopaminergic activity (for a detailed discussion, see Salamone and Correa, 2012; Richard et al., 2013). It may therefore also be questioned whether excessive food intake necessarily reflects an attempt to generate more reward in compensation for reduced mesolimbic dopamine signaling (Pothos et al., 1998; Blum et al., 2000; Volkow and Wise, 2005; Volkow et al., 2008). The mirror image of this proposition implies that increases in mesolimbic dopamine activity would lead to an inhibition of food intake because sufficient dopamine signaling suppresses the further need of more hedonic value associated with food intake. Whether or not such hedonic processes offer a possible link between the PYY_{3-36}-induced enhancement of striatal dopamine activity and inhibition of food intake is currently unknown. In view of the emerging limitations of the "common dopamine hypothesis of reward" (Salamone and Correa, 2012), however, we believe that this link cannot simply be explained by a dopamine-mediated modification of the hedonic value of food. Rather, we agree with the rich literature suggesting that immediate and unpredicted hedonic experiences ("liking") are linked only minimally to mesolimbic

dopamine signaling, and instead are more directly associated with and precipitated by opioidergic signals (Berridge et al., 2009; Richard et al., 2013).

In contrast to its limited influence on "liking," mesolimbic dopamine signaling likely plays a crucial role in "wanting," which in relation to food intake is typically conceptualized as incentive salience (Berridge et al., 2009). Incentive salience in this case is a type of motivation that promotes approach toward and consumption of rewards, and is largely mediated by subcortical neural systems that include mesolimbic dopamine projections (Berridge et al., 2009; Richard et al., 2013). Notably, "wanting" can apply to innate (unconditioned) incentive stimuli or to conditioned stimuli that were originally neutral but now predict the availability of rewarding stimuli following prior conditioning with an innate incentive stimulus (Berridge, 2007). Depending on the context, "wanting" can thus be precipitated by various neuropsychological processes, including appetitive motivation, approach behavior, reward prediction, and exertion of effort (Berridge, 2007; Berridge et al., 2009; Salamone and Correa, 2012; Richard et al., 2013). Considering these multiple possibilities, it seems obvious that the role of dopamine in "wanting" is multifaceted. As extensively reviewed elsewhere (Berridge, 2007; Berridge et al., 2009; Salamone and Correa, 2012; Richard et al., 2013), however, it appears that striatal dopamine activity generally promotes many of the neuropsychological mechanisms underlying "wanting" and thus facilitates appetitive motivation, approach behavior, reward prediction, and exertion of effort. One prediction from these findings is that the PYY_{3-36}-induced elevation of striatal dopamine activity would be associated with increased "wanting" for food, and consequently, would lead to increased food intake. But this prediction is clearly at odds with the numerous findings demonstrating reduced food intake following PYY_{3-36} treatment (**Table 1**), even if the peptide is administered before subjects have access to food (Batterham et al., 2002; Cox

and Randich, 2004; Koegler et al., 2005). Consequently, dopamine-meditated changes in "wanting" are unlikely to offer a plausible link between the PYY_{3-36}-induced enhancement of striatal dopamine activity and inhibition of food intake.

Based on the robust effects of PYY_{3-36} on central information processing and salience learning discussed above, it is tempting to hypothesize that dopamine-mediated changes in salience attribution to neutral stimuli could contribute to the inhibition of food intake by PYY_{3-36}. Indeed, increased striatal dopaminergic activity can markedly enhance the salience of stimuli, even if they are neutral and/or have previously been associated with inconsequential experiences (Berridge and Robinson, 1998; Wise, 2004). A good example is the abolition of the LI effect by dopamine-stimulating drugs. Under conditions of low dopaminergic activity, subjects who are pre-exposed to a neutral stimulus (the CS) display slower conditioning between the CS and a consequential stimulus (the US) because they learn that the CS is a weak predictor of the US. Under such conditions, non-reinforced CS pre-exposure thus diminishes the perceived salience of the CS during conditioning (Mackintosh, 1975; Lubow et al., 1981; Weiner, 2003; Lubow, 2005). Under conditions of high dopaminergic activity, however, the inhibitory influence of CS pre-exposure on CS salience is weakened, so that subjects continue to attribute high levels of salience to the CS. As a consequence, CS-pre-exposed subjects with high dopaminergic activity behave as if they have not been pre-exposed and go on to treat the CS as a novel stimulus that attracts much of their attention. As discussed above, PYY_{3-36} has a marked impact on such salience learning, with PYY_{3-36}-treated animals attributing high levels of salience to previously pre-exposed neutral stimuli. One may therefore predict that PYY_{3-36} administration before or even during access to food could alter salience or "attractiveness" of food and shift the subject's attentive resources away from food to other stimuli that are present at the time of food intake. Such a shift

may direct attention to internal perceptive processes or to extraneous external stimuli such as visual, auditory, or social cues that are present in the context in which food consumption occurs. While this hypothesis is novel in the context of PYY_{3-36}, similar concepts have been forwarded by others in other contexts. For example, it has been suggested that AMPH-induced hypophagia is not caused primarily by loss of appetite, but rather by an altered brain state in which animals cannot respond selectively (Heffner et al., 1977; Cannon et al., 2004). These postulated dopamine-mediated processes await verification. Moreover, by no means do we speculate that the PYY_{3-36}-induced effects on food intake are primarily or solely driven by the peptide's pro-dopaminergic effects as gastrointestinal peptides typically engage multiple processes to control food intake (Schwartz et al., 2000; Rüttimann et al., 2009; Berthoud, 2011; Woods and Ramsay, 2011; Woods and Langhans, 2012; Begg et al., 2013). Rather, our view is that the pro-dopaminergic effects of PYY_{3-36} are a likely contributing factor to the inhibition of food intake and may provide an intriguing link between the peptides' effects on food intake and other behaviors.

8. Physiological versus pharmacological effects of PYY_{3-36}

One important question that remains to be answered by future investigations relates to the physiological relevance of the effects of PYY_{3-36} on behavioral and cognitive functions. It remains currently unknown whether the aforementioned behavioral and cognitive changes induced by peripheral PYY_{3-36} administration may primarily represent pharmacological effects, or alternatively, whether they also have physiological relevance. The current knowledge does not allow an evidence-based answer to this question with respect to behavior and cognition. However, numerous findings in both

humans and rodents strongly support a physiological role of PYY_{3-36} in the control of food intake.

For example, genetically modified mice that lack PYY develop an obesity phenotype (Batterham et al., 2006; Boey et al., 2006), indicating that endogenous PYY signaling contributes to energy homeostasis and related metabolic processes. This hypothesis is further strengthened by the observation that obese individuals display attenuated circulating levels of PYY (Batterham et al., 2003; Chandarana et al., 2011). Moreover, various human and animal studies in wwhich exogenous PYY_{3-36} was administered in different regimens and in which post-prandial physiological levels were mimicked, efficiently reduced food intake and attenuated body weight gain (reviewed in Chandarana and Batterham, 2008; Kirchner et al., 2010).

Another important piece of evidence supporting a physiological role of PYY_{3-36} in the control of food intake stems from recent functional neuroimaging studies demonstrating that physiological levels of $PYY_{3-36,}$ besides activating homeostatic brain areas such as the hypothalamus, also activate numerous other cortical and subcortical brain areas, some of which play crucial roles in central reward processing (Batterham et al., 2007; De Silva et al., 2011; Weise et al., 2012). For example, Batterham et al. (2007) observed that exogenous PYY_{3-36} infusion in humans, which resulted in circulating PYY_{3-36} concentrations that were similar to those observed post-prandially, modulated neuronal activity within corticolimbic and higher cortical brain areas, including hypothalamus, striatum, and orbitofrontal cortex. While highlighting extra-hypothalamic effects of PYY_{3-36} at physiologically relevant concentrations, the data also highlight the possibility that physiological concentrations of PYY_{3-36} modulate behavioral functions beyond food intake. As mentioned above, however, the latter hypothesis awaits direct exploration by

future investigations ascertaining possible behavioral and cognitive effects of exogenous PYY_{3-36} treatment at physiologically relevant concentrations.

Related to this, it remains essentially unknown whether (physiological) variations in plasma PYY_{3-36} levels, be it after short-term food restriction or in the post-prandial state, could influence behavioral and cognitive functions such as incentive salience, short-term memory, and/or sensorimotor gating. Most studies that explored the behavioral effects of dietary modulations such as food restriction or binge-eating were based on experimental designs in which the dietary manipulation was chronic (Inoue et al., 2004; Carlini et al., 2008; Khabour et al., 2010; Labouesse et al., 2013). Under such conditions, the behavioral changes could readily be attributable to a broad spectrum of factors, including long-term neuronal and neurochemical adaptations. Moreover, among the few studies that investigated possible behavioral modifications following short-term food restriction (Inoue et al., 2004; McLaughlin et al., 2011; Rajab et al., 2014), none directly correlated the behavioral outcomes with plasma PYY3-36 levels. Therefore, additional studies are clearly warranted in order to explore whether (physiological) variations in plasma PYY_{3-36} levels can exert a significant influence of multiple behavioral and cognitive functions akin to the effects induced by peripheral PYY_{3-36} administration. The inclusion of genetically modified animals such as mice deficient for PYY (Batterham et al., 2002) and the Y2 receptor (Baldock et al., 2002; Karl et al., 2010) may help provide answers for these open questions.

Such attempts would also help discern the Y receptor subtypes that mediate the behavioral and cognitive effects of exogenous PYY_{3-36} treatment (Stadlbauer et al., 2013b, 2014). Since PYY_{3-36} is a high-affinity Y2 receptor ligand (Walther et al., 2011), it is believed that the effects of peripheral PYY_{3-36} administration on behavioral and cognitive functions primarily involve signaling at the Y2 receptor (Stadlbauer et al.,

2013b, 2014). This hypothesis would indeed be in agreement with findings obtained in the context of food intake: Mice deficient of the Y2 receptor are resistant to the anorectic effect of exogenous PYY_{3-36} (Batterham et al., 2002), and pharmacological blockade of the Y2 receptor using a selective Y2 receptor antagonist abolishes the anorectic actions of PYY_{3-36} in rats (Abbott et al., 2005). At high concentrations, however, PYY_{3-36} may also bind to other Y receptor subtypes that are expressed in the CNS, including the Y1 receptor (Stanic et al., 2011). It thus remains to be explored whether the effects of exogenous PYY_{3-36} treatment on incentive salience, short-term memory, and sensorimotor gating (Stadlbauer et al., 2013b, 2014) may be mediated by signaling at multiple Y receptor subclasses, or whether these may represent selective Y2 receptor-mediated effects.

9. Concluding remarks

Examining the effects of exogenous PYY_{3-36} in animal models has revealed that this gut-derived peptide influences a wide spectrum of behavioral and cognitive functions. Hence, the behavioral effects of PYY_{3-36} are not restricted to the control of food intake and regulation of energy homeostasis. Rather, they extend to numerous other functional domains such as central information processing, salience learning, working memory, and behavioral responding to novelty and dopamine-stimulating drugs. Whether PYY_{3-36}'s effects on food intake and other behaviors are somehow interrelated remains unanswered and warrants further investigation. One intriguing possibility is that PYY_{3-36}-induced changes in dopaminergic activity may bridge diverse behavioral manifestations to elicit inhibitory effects on food intake. The continuous integration of behavioral and cognitive neuroscience with research on food intake and metabolism may therefore be a particularly fruitful approach to address these open questions as it

may offer a heuristic appreciation of the interactions between gut-derived signals, energy homeostasis, reward, and behavioral adaptations.

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Tables and figures

Species	Route of administration	Food intake	References
Rat	Intraperitoneal (acute)	↓	Batterham et al., 2002; Cox et al., 2004; Nordheim et al., 2004.
	Intraperitoneal (chronic)	↓	Batterham et al., 2002; Chelikani et al., 2007;
	Intravenous (acute)	↓	Chelikani et al., 2005; Stadlbauer et al., 2013.
	Subcutaneous (chronic)	↓	Pittner et al., 2004.
Mouse	Intraperitoneal (acute)	↓	Challis et al., 2003; Halatchev et al., 2005; Martin et al., 2004; Pittner et al., 2004.
	Subcutaneous (chronic)	↓	Pittner et al., 2004.
Non-human primates	Intramuscular (acute)	↓	Moran et al., 2005.
	Intravenous (acute)	↓	Koegler et al., 2005.
Human	Intravenous (acute)	↓	Batterham et al., 2002; Degen et al., 2005; le Roux et al., 2008.

Table 1. A summary of the inhibitory effects of peripheral PYY_{3-36} administration on food intake in various species. As summarized and discussed in detail elsewhere (Manning and Batterham, 2014), there are also studies reporting no significant effects of peripheral PYY_{3-36} administration on food intake.

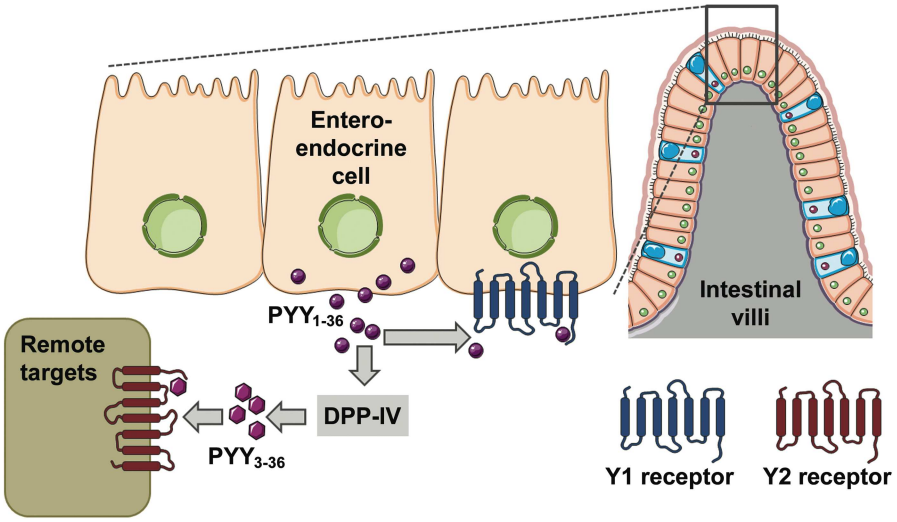

Figure 1. Simplified schematic illustration of the sites of production and action of PYY. PYY_{1-36} is mainly released from distal intestinal enteroendocrine L-cells in response to luminal nutrient stimulation. PYY_{1-36} can exert paracrine actions on neighboring cells by activating Y1 receptors. In the blood, PYY_{1-36} is rapidly converted to PYY_{3-36} by the ubiquitously expressed enzyme, dipeptidyl-peptidase IV (DPP-IV), which cleaves the two N-terminal amino acids. Circulating PYY_{3-36} exerts endocrine functions and can influence remote targets such as the central nervous system by activating the Y2 receptor. Modified from Schwartz and Holst, 2010.

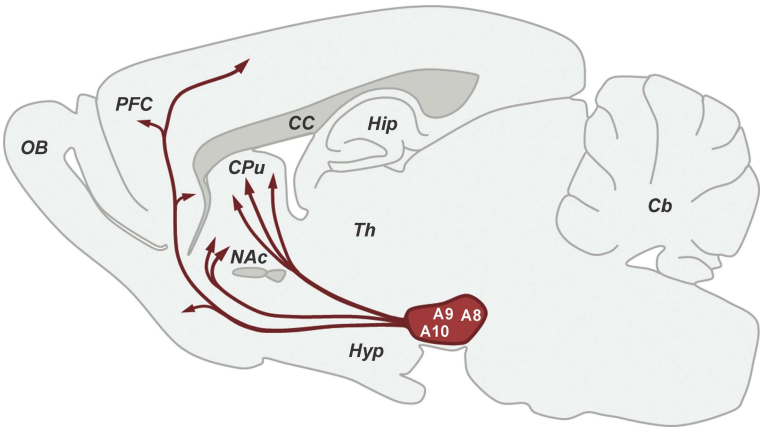

Figure 2. Schematic illustration of midbrain dopamine cell groups and their projections in rodents. A large population of dopamine cells are localized in discrete cell groups (A8-A10) of the ventral midbrain. The majority of A10 dopamine cells form the ventral tegmental area (VTA) and project to cortical areas such as the prefrontal cortex (PFC) and to limbic areas such as the nucleus accumbens (NAc), hypothalamus (Hyp), and amygdala (not shown). These projections form the mesocortical and mesolimbic dopamine pathways, respectively. A9 dopamine cells form the substantia nigra pars compacta (SNc) and project to dorsal parts of the striatum (= caudate putamen, CPu), giving rise to the nigrostriatal dopamine pathway. The A8 cell group forms a dorsal and caudal extension of the A9 cell group and contains cells that project to both striatal, limbic and cortical areas. Other dopamine cell groups such as those found in hypothalamic (A11 and A12), preoptic (A14), and olfactory (A16) areas are not shown. Cb, cerebellum; CC, corpus callosum; Hip, hippocampus; OB, olfactory bulb; Th, thalamus.

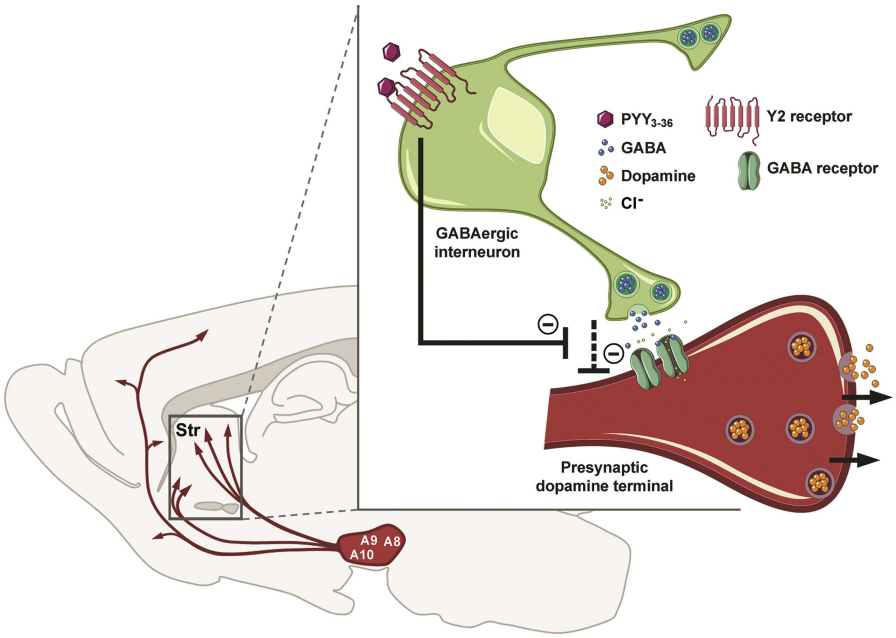

Figure 3. Proposed model by which PYY_{3-36} induces hyperdopaminergic states in striatal areas. GABAergic interneurons (green) located in the striatum (Str) tonically inhibit striatal dopamine terminals (red). Activation of GABA receptors on dopamine fibers causes chloride ion (Cl^-) influx and consequently results in hyperpolarization of presynaptic dopamine terminals. PYY_{3-36}-induced activation of Y2 receptors located on striatal GABAergic interneurons reduces the neural activity of GABAergic cells, which in turn weakens their inhibitory inputs onto presynaptic dopamine terminals. The PYY_{3-36}-induced attenuation of this fast-forward inhibitory mechanism facilitates the release of dopamine (as indicated by the black arrows).

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