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REVIEW

Imaging neuropeptide effects on human brain function

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Abstract

The discovery of prosocial effects of oxytocin (OT) opened new directions for studying neuropeptide effects on the human brain. However, despite obvious effects of OT on neural responses as reported in numerous studies, other peptides have received less attention. Therefore, we will only briefly summarize evidence of OT effects on human functional magnetic resonance imaging (fMRI) and primarily focus on OT's sister neuropeptide arginine-vasopressin by presenting our own coordinated-based activation likelihood estimation meta-analysis. In addition, we will recapitulate rather limited data on few other neuropeptides, including pharmacological and genetic fMRI studies. Finally, we will review experiments with external neuropeptide administration to patients afflicted with mental disorders, such as autism or schizophrenia. In conclusion, despite remaining uncertainty regarding the penetrance of exogenous neuropeptides through the blood-brain barrier, it is evident that neuropeptides simultaneously influence the activity of limbic and cortical areas, indicating that these systems have a good potential for therapeutic drug development. Hence, this calls for further systematic studies of a wide spectrum of known and less known neuropeptides to understand their normal function in the brain and, subsequently, to tackle their potential contribution for pathophysiological mechanisms of mental disorders.

Keywords Neuropeptides · Human · fMRI · ALE · Oxytocin · Vasopressin

Introduction

Neuropeptides are a class of molecules that modify brain activity in a different manner than "classical" neurotransmitters, such as glutamate and GABA. Indeed, the release of neuropeptides requires a generation of hundreds action potentials, resulting in exocytosis of a single secretory vesicle from axons (Chini et al. 2017). Remarkably, the neuropeptide content of even a single granule is capable to effectively bind to respective G-coupled receptors on target neurons, initiating intracellular pathways to change cell excitability (Chini et al. 2017). This mode of action is in accordance with their neuromodulatory role as they regulate basic functions such as stress, pain, or appetite, linking brain activity to the physiological state of the whole body (van den Pol 2012).

Because of these characteristics, neuropeptides and their receptors constitute interesting targets for the development of new molecule-modifying behaviors in the context of psychiatric disorders, for which we have now only few and not fully efficient drugs. Furthermore, translational research in animals has confirmed this potential, and several attempts have already been conducted in humans. Although some results are encouraging, the differences between patients and animal models of disease have so far prevented real progress.

Here, we review studies that have investigated the role of neuropeptides in the regulation of human brain activity. Using functional magnetic resonance imaging (fMRI) in combination with pharmacological administration or gene polymorphism screening, researchers have been able to unveil the cerebral regions on which neuropeptides act. We start by discussing oxytocin (OT), as this neurohormone has received much attention recently; secondly, we present the results of a coordinated-based meta-analysis of its sister neuropeptide arginine-vasopressin (AVP); finally, we review studies on other less "popular" molecules and their receptors, such as

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neuropeptide S (NPS), neuropeptide Y (NPY), cholecystokinin (CCK), and corticotropin-releasing hormone (CRH). Although neuropeptides influence a wide spectrum of functions, most of the focus has been directed at the study of social behavior, more precisely how humans perceive, evaluate, and respond to social interaction (Ruff and Fehr 2014).

Oxytocin

OT is by far the most studied neuropeptide in humans. This comes from its effects on social behavior and the consequent hopes of pharmacologic therapy for psychiatric disorders it has raised (Lefevre and Sirigu 2016). Because OT is the major focus of this special issue, we will only summarize two recent coordinated-based quantitative meta-analyses of OT effects on human brain activity. The first one included 11 studies and reported a significant modulation of BOLD signal following intranasal (IN) OT administration, which mapped to the insula, a region involved in emotion regulation (Wigton et al. 2015). Other regions, such as the amygdala, were also often reported, but no significant effect was found in the meta-analysis. The second meta-analysis included 66 studies from both healthy and clinical populations (Wang et al. 2017). The authors found that OT significantly induced both decrease and increase in amygdala responses of healthy patients (35 studies), as well as increased activity in the caudate nucleus and the superior temporal gyrus. In patients with autism, social anxiety, post-traumatic stress disorders, or borderline personality disorders, only a decrease in BOLD in the amygdala was statistically significant (7 studies). When comparing patients to healthy subjects, it was found that OT decreased activity in the amygdala in healthy subjects to a greater degree than in patients, regardless of their affliction, suggesting that OT exerts distinct effects on healthy subjects and patients afflicted with psychiatric conditions. Finally, it should be noted that it remains yet unknown how IN OT exerts its effects (see the "Application of exogenous neuropeptides" section for more details), and thus these results need to be interpreted with caution. Taken together, IN OT has been consistently found to modulate the activity of limbic regions, such as the amygdala and the insula, an effect that has been reproduced to some extent in clinical cohorts (Domes et al. 2013; Gordon et al. 2013; Aoki et al. 2014), although more studies are required for reaching more definite conclusions. Importantly, the type of behavioral paradigm (e.g., appetitive vs. aversive) employed for task-dependent fMRI has an impact on the effect of OT, leading to increases or decreases of BOLD signal (Wang et al. 2017), which is consistent with the idea that this neurohormone has a context-dependent type of action (Bartz et al. 2011). In addition, sex may play an important role, perhaps reflecting differences in basic endogenous OT concentrations or differences in sensitivity to exogenous OT, which could be related to interactions with sex hormones. The context- and sex-dependent effects of IN OT underscore the need for rigorous dose-response (Spengler et al. 2017) and sex hormone interaction studies (Choleris et al. 2008).

Vasopressin

AVP is a nonapeptide differing from OT by only two amino acids. It is synthetized in the same regions of the hypothalamus, namely the paraventricular, supraoptic, and accessory nuclei (Ludwig and Leng 2006). While AVP exerts rather distinct effects at the peripheral level than OT, it has similarly been involved in the central modulation of social behaviors (Caldwell et al. 2008). More precisely, AVP and OT are two peptides that share a common origin from an evolutionary point of view, as several species only have one equivalent fulfilling the same roles (Banerjee et al. 2016). In mammals, it appears that OT and AVP often exert opposite effects on social behavior (Carter and Altemus 1997), with OT promoting social behavior and AVP antagonizing them, although this vision is oversimplified, as AVP effects have been subsequently found to be both pro- and anti-social, with large variations between species and sex (Dumais and Veenema 2015).

In humans, AVP administration is done, as for OT, via IN spray application, which is subjects to the same critics (see the "Application of exogenous neuropeptides" section). Nevertheless, behavioral modifications after IN AVP have been reported, such as emotion processing (Guastella et al. 2010), and more generally, social cognition, at least in males (McCall and Singer 2012). Furthermore, alterations of AVP receptor gene have been linked to social traits, as evident in cooperation and competition games, and to some psychiatric disorders such as autism and major depression (Aspé-Sánchez et al. 2015). However, there are some discrepancies in behavioral effects of AVP on rodents vs. human: while AVP has been shown to regulate amygdala and striatum activity in rodents (Huber et al. 2005; Galbusera et al. 2017), these regions have not been found influenced by AVP in humans (see the meta-analysis hereafter). Other areas thought to be affected by AVP, at least in rodents, include the lateral septum and hippocampus (Febo and Ferris 2014; Stoop 2014). Furthermore, the CA2 region of the hippocampus has been shown to be regulated by both OT and AVP, suggesting interactive effects on social memory (Smith et al. 2016b; Raam et al. 2017).

As stated in the "Oxytocin" section, OT has already been reviewed extensively by others; however, its close cousin AVP has not received as much attention and no one so far has conducted a rigorous meta-analysis of pharmaco-fMRI studies involving AVP. For the present review, we performed our own meta-analysis of all existing studies that have investigated the effects of AVP on brain activity in humans engaged in some form of social behavior. For this purpose, we used the

PubMed database to identify fMRI experiments involving IN AVP administration. Searching for the keywords "vasopressin" AND "fMRI", we found 423 studies published by March 2018. Out of this first-level literature search, we identified 14 original studies in which AVP was administered IN to healthy men before undergoing an fMRI scan. Because AVP has sexually dimorphic effects (Rilling et al. 2013), we selected only those studies performed on male volunteers. Next, we eliminated five studies due to their restrictions on regions of interest or functional connectivity analysis, leaving nine studies for our activation likelihood estimation (ALE) analysis (Zink et al. 2010, 2011; Rilling et al. 2012; Brunnlieb et al. 2013a, b, 2016; Lee et al. 2013; Feng et al. 2015; Gozzi et al. 2017). The main effects on brain activity and behavior reported by each study are summarized in Table 1.

Because of the limited available data and in order to best summarize the effects of IN AVP, we conducted the ALE meta-analysis on all data, collapsing between and within subject designs, the type of behavioral tasks employed (which mainly involved cooperative games and emotion processing paradigms) and the direction of signal change. All nine studies were double-blind and placebo-controlled. To perform our coordinate-based meta-analysis, we applied the revised ALE algorithm (Turkeltaub et al. 2012) of GingerALE (https://www.brainmap.org/ale/), as described in details elsewhere (Eickhoff et al. 2012). Accordingly, we used default parameters that GingerALE selects automatically for the optimum FWHM; the statistical threshold was set at $p < 0.001$ uncorrected, with a cluster size of > 150 mm^3. The resulting analysis included 347 subjects and 65 reported coordinates and revealed three clusters located in the frontal cortex (Brodmann areas 8, 9, and 47; Fig. 1). Note that apart from the volume threshold, no statistical correction was employed at the cluster level.

Although the result of our analysis needs further confirmation on a larger number of studies, it suggests that IN AVP modulates cortical areas during social behavior. It can be proposed that other areas, which could not be found with the present analysis due to the limited amount of studies, are also being modulated by AVP, perhaps in a behavior-dependent manner.

In contrast to OT, we did not find any studies testing IN AVP in a psychiatric population. The only one report suggesting a link between the AVP-ergic system and social behavior disorders found that several single nucleotide polymorphisms of the AVP 1b receptor were associated with autism (Francis et al. 2016).

In conclusion of this section, it can be speculated that AVP modulates human brain activity and behavior, and hence, the AVP system may be interesting as a therapeutic target for psychiatric disorders. However, further investigation of the capacity of AVP or its derivatives to cross the blood-brain barrier (BBB) are required. In this line, a recent study used an oral AVP1aR antagonist in patients with autism but obtained mixed results (Umbricht et al. 2017).

Table 1 Summary of the main effects (AVP vs. placebo) reported by the fMRI studies included in the ALE analysis. All subjects were adult healthy men. *R*, right; L, left. In some cases, no behavioral outcomes were recorded, or were not relevant (performance on easy tasks, reaction time, etc.), as paradigms employed simply consisted in stimuli presentation

Reference	Subjects and design	Dose of IN AVP (IU)	Behavioral task	Behavioral effects	fMRI effects
Brunnlieb et al. 2013a	36 subjects (age = 20.7), between-subjects design	20	Taylor aggression paradigm	None	↑ R temporal sulcus
Brunnlieb et al. 2013b	42 subjects (age = 25.8), between-subjects design	20	Socio-emotional perception	Not measured	↑ R amygdala, R parahippocampal gyrus, cingulate cortex
Brunnlieb et al. 2016	34 subjects (age = 24,3), between-subjects design	20	Stag hunt task	Enhanced cooperation	↓ L dlPFC
Feng et al. 2015	93 subjects (age = 20.7), between-subjects design	20	Prisoner's dilemma	None	Neuroticism correlated with AVP modulation of L lateral temporal lobe, ACC, R insula
Gozzi et al. 2017	21 subjects (age = 26.04), within-subjects design	40	Social feedback	Not relevant	↓ L temporoparietal junction, R fusiform, ACC, mPFC
Lee et al. 2013	19 subjects (age not specified), between-subjects design	40	Emotion perception	Not measured	↓ R amygdala
Rilling et al. 2012	59 subjects (age = 20.2), between-subjects design	20	Prisoner's dilemma	Enhanced cooperation	Both ↑ and ↓ in many clusters of PFC
Zink et al. 2010	20 subjects (age = 28.6), within-subjects design	40	Face-matching task	Not relevant	↑ subgenual cingulate
Zink et al. 2011	20 subjects (age = 28.6), within-subjects design	40	Social-matching task	Not relevant	↓ L temporoparietal junction

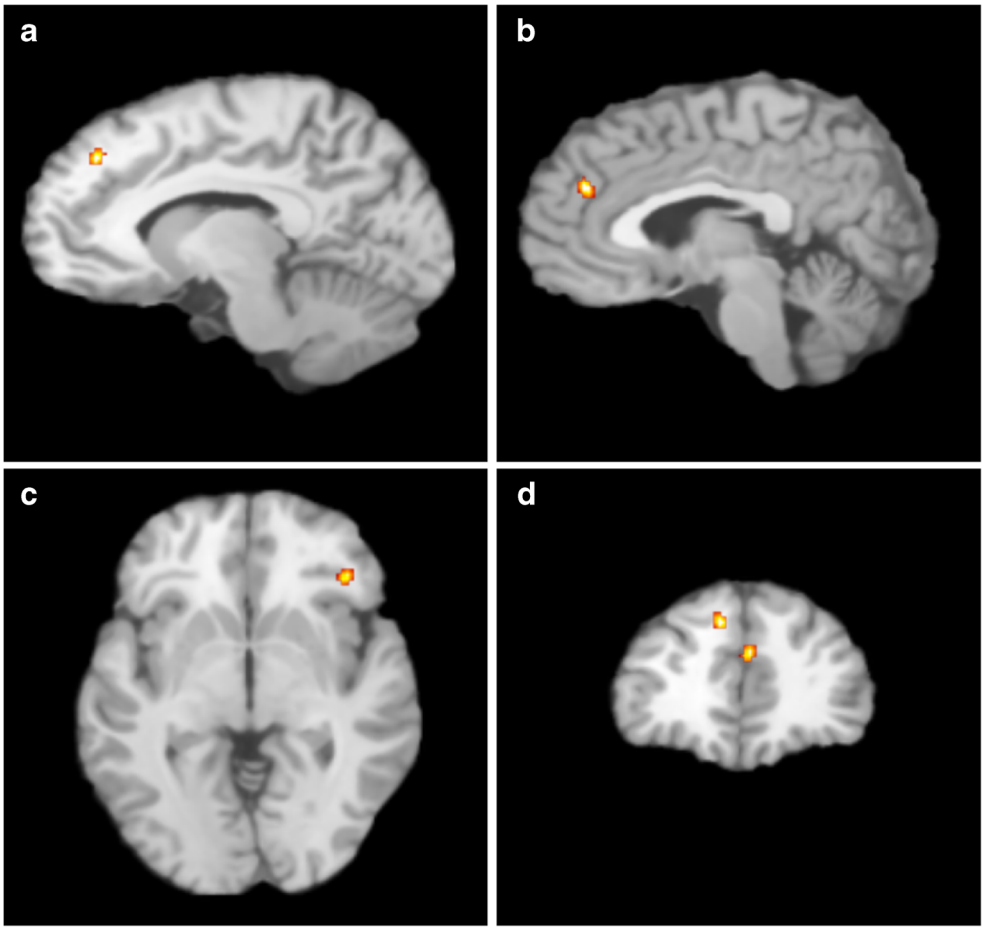

Fig. 1 General effects of IN AVP on the human male brain activity. Three clusters exceeding 200 mm^3 were found at the following: 4 39 25 (**a** and **d**), 39 29 − 4 (**c**), and − 8 37 39 (**b** and **d**) (Laird et al. 2011). Each of these clusters had two contributors

Other neuropeptides

Although OT (and to a lesser extent AVP) have attracted most of the attention up to date, the family of neuropeptides comprises almost 300 members (according to this recent database (60 of them with a PMID): http://isyslab.info/NeuroPep/) (Wang et al. 2015), but the function of a vast majority of them remains enigmatic in mammals. In respect to the human brain activity, only few studies were focused on the direct effects of systemically applied neuropeptide or on the association between gene polymorphism of neuropeptide receptors and BOLD signal in specific regions. Here, we summarize these very limited but valuable findings.

Neuropeptide S (NPS) is a peptide produced mainly, but not exclusively, in anxiety and sleep-related brainstem region such as the locus coeruleus, it is also moderately expressed in forebrain regions like the amygdala. In rats, central administration of NPS increases arousal and simultaneously attenuates anxiety by acting on its unique cognate receptor NPSR (Xu et al. 2004). In analogy, one variation of human NPS receptor gene have been associated with stress and anxiety levels (Pape et al. 2010). More precisely, a codon switch (Asn(107)Ile) due to a single nucleotide polymorphism rs324981 A/T is modifying the NPSR expression level as well as the NPS efficacy at NPSR. To date, four fMRI studies have found a significant effect of this gene polymorphism on the activity of several brain regions, including anterior cingulate cortex (Domschke et al. 2011), amygdala (Dannlowski et al. 2011; Streit et al. 2014), and connectivity of amygdala with other limbic regions including insula and medial prefrontal cortex (mPFC) (Domschke et al. 2017).

Interestingly, mPFC activity was also found to depend on NPS receptor gene variation, as revealed by near-infrared spectroscopy (Guhn et al. 2015), and even glutamate levels in the anterior cingulate cortex were found to be influenced by the allele of the NPS receptor gene (Ruland et al. 2015). The results of the above-mentioned studies were obtained during tasks in which subjects were exposed to fearful faces, further pointing at the specific role of NPS in anxiety regulation. Interestingly, it was recently demonstrated that NPS exerts at least some of its anxiolytic action via the oxytocinergic system (Grund et al. 2017). This line of research suggests that NPS might be a promising target for the treatment of anxiety disorders, as it may tune down several limbic regions important for the expression of defensive behavior.

In contrast to NPS, the cholecystokinin tetrapeptide (CCK) is known to induce panic attacks following peripheral administration in humans (Zwanzger et al. 2012). In this line, two

fMRI studies have consistently reported that intravenous injection of CCK provoked strong activation of panic-related areas, such as the cingulate cortex, several other cortical regions like the superior frontal gyrus and the medial temporal gyrus, the amygdala, and regions of the brain stem (pons and midbrain) (Schunck et al. 2006; Eser et al. 2009). It is possible that these effects are modulated, or counterbalanced, by the NPS system, although this remains to be investigated (Ruland et al. 2015). Thus, further studies are required to elucidate potential interactions of NPS and CCK and their opposite modulation of anxiety-related brain regions.

Another neuropeptide, which is involved in the modulation of stress responsiveness, is neuropeptide Y (NPY). It is composed of 36 amino acids and widely expressed in the brain, particularly in amygdala and striatum (Adrian et al. 1983). Consequently, it was found that the NPY haplotype specifically influences the expression of NPY and subsequently the activity of human amygdala and nucleus accumbens in response to the induction of stress by painful stimuli (Zhou et al. 2008). Other studies have found that NPY haplotype modulated BOLD signal in mPFC and cingulate cortex in reaction to pain-induced stress (Mickey et al. 2011; Opmeer et al. 2014). To summarize, specific genetic variations (haplotype) lead to low levels of NPY expression, which in turn increases neural responsivity and physiological reaction to stressful stimuli. This also suggests that pharmacological manipulations of the NPY system could have a beneficial impact on stress and anxiety-related disorders.

Still in the attempt to alleviate pain and stress, other leads have been so far unsuccessfully explored; for instance, substance P or CRH (Borsook et al. 2012; Contoreggi 2015). In the case of CRH, significant efforts have been conducted in the attempt to develop a pharmacological agent against stress and anxiety. But while preclinical studies on rodents were promising, results in humans were not as conclusive (Refojo and Holsboer 2009; Sanders and Nemeroff 2016).

Application of exogenous neuropeptides

First, it should be noted that neither IN OT nor IN AVP have been reported to produce side effects, and subjects are typically unable to identify correctly whether they received the treatment or the placebo. Secondly, it still remains unclear how exogenously applied neuropeptides reach the brain via the nasal route (Leng and Ludwig 2015). There have been several reports in rodents suggesting that IN OT increases brain concentration of OT (Neumann et al. 2013; Tanaka et al. 2018), which were not fully confirmed in monkeys (Dal Monte et al. 2014; Modi et al. 2014; Freeman et al. 2016; Lee et al. 2017). In humans, IN OT or AVP remains conflicting especially in terms of temporal kinetics when looking at cerebrospinal fluid concentrations following administration (Born et al. 2002; Striepens et al. 2013). Given the reported effects of neuropeptides on BOLD signals in human brain, several hypotheses have been proposed on how IN administration could produce these effects (Quintana et al. 2014). First, OT and AVP could pass the epithelium and undergo retrograde transport via the olfactory or trigeminal nerves. A second hypothesis is that OT can reach the subarachnoid space and diffuse from there subsequently into the brain, although no mechanistic explanation has been brought so far. Finally, it has not been ruled out that IN OT could exert its effect via peripheral action as OTR are "disseminated" through our body, including skin, heart, vasculature, gut, lungs, and other organs (Poisbeau et al. 2017). Thus, it can be speculated that IN OT activates ascending sensory and autonomic pathways converging via the brainstem either onto the forebrain areas or inducing activation of OT neurons to release the neuropeptide endogenously. This has given researchers the idea of using endogenous molecules known to stimulate OT release. For instance, alpha melanocyte stimulating hormone (alpha-MSH) has been shown to activate OT neurons and provoke dendritic release of OT (Sabatier et al. 2003; Paiva et al. 2017), and to induce prosocial behavior in rodents (Modi et al. 2015). Hence, clinical trials are now being envisaged in which patients would receive an oral agonist to alpha-MSH receptor 4 (Johnson and Young 2017). While interesting, it should be noted that this approach might be ultimately limited by the role of alpha-MSH in energy homeostasis. Another promising area of research will be the development of non-peptide ligands that can cross the blood-brain barrier and act on brain neuropeptide receptors.

Conclusion

Human fMRI studies support numerous reports on mammals, including primates, demonstrating the important role of neuropeptides in the modulation of socio-emotional behaviors. However, further studies are largely limited by the unsolved question about the penetrance of exogenously applied neuropeptides, exemplarily OT, through the blood-brain barrier in primates (please see the article of Mary Lee in this special issue). In addition, there is a need for more dose-response experiments, as for now the typical amount administered is supra-physiological (Leng and Ludwig 2015). Therefore, further studies, especially on primates, are essential for understanding the anatomy and physiology of neuropeptide systems and their specific role in the pathophysiology of mental disorders. In addition to fMRI, the development of PET ligands specific to neuropeptidergic systems will allow to investigate neuropeptides receptors localization and potential pharmacologic drugs mechanisms of action in vivo (Smith et al. 2016a). In this line, PET scans have already been used to investigate interactions between neuropeptides and other transmitters (Striepens et al. 2014; Lefevre et al. 2017).

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