Neuroscience and Biobehavioral Reviews 73 (2017) 255–275

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Is there a role for ghrelin in central dopaminergic systems? Focus on nigrostriatal and mesocorticolimbic pathways

Alicia Stievenard[a,1], Mathieu Méquinion[b,1], Zane B. Andrews[b], Alain Destée[a], Marie-Christine Chartier-Harlin[a], Odile Viltart[a,1], Christel C. Vanbesien-Mailliot[a,*,1]

[a] Univ. Lille, Inserm, CHU Lille, UMR-S 1172 – JPArc – Centre de Recherche Jean-Pierre AUBERT Neurosciences et Cancer, F-59000 Lille, France
[b] Department of Physiology, Monash University, Clayton, Victoria 3800, Australia

ARTICLE INFO

Article history:
Received 29 July 2016
Received in revised form
23 November 2016
Accepted 25 November 2016
Available online 30 November 2016

Keywords:
Anorexia nervosa
Dopamine
Ghrelin
Goal-directed action
Motivation
Parkinson's disease

ABSTRACT

The gastro-intestinal peptide ghrelin has been assigned many functions. These include appetite regulation, energy metabolism, glucose homeostasis, intestinal motility, anxiety, memory or neuroprotection. In the last decade, this pleiotropic peptide has been proposed as a therapeutic agent in gastroparesis for diabetes and in cachexia for cancer. Ghrelin and its receptor, which is expressed throughout the brain, play an important role in motivation and reward. Ghrelin finely modulates the mesencephalic dopaminergic signaling and is thus currently studied in pathological conditions including dopamine-related disorders. Dopamine regulates motivated behaviors, modulating reward processes, emotions and motor functions to enable the survival of individuals and species. Numerous dopamine-related disorders including Parkinson's disease or eating disorders like anorexia nervosa involve altered ghrelin levels. However, despite the growing interest for ghrelin in these pathological conditions, global integrative studies investigating its role in brain dopaminergic structures are still lacking. In this review, we discuss the role of ghrelin on dopaminergic neurons and its relevance in the search for new therapeutics for Parkinson's disease- and anorexia nervosa-related dopamine deficits.

Contents

* Corresponding author at: INSERM UMR-S 1172/JPArc – Team "Early stages of Parkinson's disease", Bat. IRCL – 1 Place de Verdun, FR-59045 LILLE Cedex, France.
E-mail addresses: alicia.stievenard@inserm.fr (A. Stievenard), mathieu.mequinion@monash.edu (M. Méquinion), zane.andrews@monash.edu (Z.B. Andrews), a-destee@chru-lille.fr (A. Destée), marie-christine.chartier-harlin@inserm.fr (M.-C. Chartier-Harlin), odile.viltart@inserm.fr (O. Viltart), christel.vanbesien@inserm.fr (C.C. Vanbesien-Mailliot).
[1] These authors equally contributed to this work.

http://dx.doi.org/10.1016/j.neubiorev.2016.11.021
0149-7634/

1. Introduction

Dopamine is a key neuromodulator involved in motivated behaviors, such as feeding, reproduction, the search for a refuge or the flight from a predator. It therefore plays a central role in the survival of species and individuals. Brain areas implicated in the control of such behaviors have been submitted to high selection pressure and were highly conserved across evolution (O'Connell and Hofmann, 2012). These structures, initially identified in rats in 1964 (Dahlström and Fuxe, 1964) and mapped in 1971 (Ungerstedt, 1971), contain dopaminergic neurons and were described not only in mammals, but also in fish, reptiles and birds (O'Connell and Hofmann, 2012; Yamamoto and Vernier, 2011). The number of tyrosine hydroxylase-positive cells, the rate-limiting enzyme of dopamine biosynthesis, is 20–30 000 in mice and 400–600 000 in humans, a difference associated with the expansion of dopaminergic fibers, in particular in the human and non-human primate neocortices (Björklund and Dunnett, 2007; Oades and Halliday, 1987).

Dopaminergic neurons originate from a population of progenitor cells located on the mesencephalic floor plate in rodent embryos, namely the ventral aqueductal ventricular zone (Gates et al., 2006; Hu et al., 2004; Ono et al., 2007; Vitalis et al., 2005). After differentiation, these neurons migrate to form different subgroups of dopaminergic neurons: among them, the A9 group is located in the substantia nigra *pars compacta* (SNc), and the A10 group in the ventral tegmental area (VTA; Björklund and Dunnett, 2007; Ferreira et al., 2008). SNc dopaminergic neurons send projections to the dorsal striatum within the nigrostriatal pathway and are involved in the control of voluntary movements. VTA dopaminergic neurons project to the ventral striatum containing the accumbens nucleus, as well as to the amygdala and the pre-frontal cortex *via* the mesocorticolimbic pathway (see Fig. 1). The VTA is known for its role in reward and motivational behaviors. Thus, in addition to their anatomical proximity and shared dopaminergic neurochemistry, VTA and SNc both contribute to the fine tuning of motivated behaviors. The mesocorticolimbic pathway provides the motivation to act whereas the nigrostriatal pathway modulates voluntary movements needed to reach the goal.

The appropriate functioning of both dopaminergic circuits contributes to this similar general goal, namely the adaptation to the environment and the maintenance of homeostasis. Their deregulation in humans leads to dysfunctions such as voluntary movement disorders in the case of the nigrostriatal pathway, and alterations of reward or motivational regulation for the mesocorticolimbic system (Berridge and Kringelbach, 2015; Lees et al., 2008; Missale et al., 1998). In this view, dopaminergic neuronal death occurring within the SNc in Parkinson's disease (PD) and the resulting decrease in striatal dopamine concentrations are responsible for the classical motor phenotype associated to this disorder: bradykinesia, rigidity and resting tremor (Błaszczyk, 1998; Postuma et al., 2015). Similarly, abnormalities in mesocorticolimbic dopaminergic neuronal function impair motivation and reward processes and contribute to pathological conditions such as depression, apathy and addictive-compulsive behaviors (Lammel et al., 2014). Due to their above-mentioned anatomical proximity and shared neurochemistry, drug modulation of one dopaminergic pathway will affect the other. For instance, dopamine agonists used to alleviate motor symptoms in PD patients can trigger a hyperactivity of dopaminergic VTA targets (Vaillancourt et al., 2013). As a consequence, patients under dopaminergic drugs, mainly dopamine agonists, can suffer from impulse control disorders (Sáez-Francàs et al., 2016). However, the interactions between these two dopaminergic pathways are not fully understood yet. Interestingly, SNc and VTA dopaminergic neurons share an additional feature since they both express receptors for the orexigenic hormone ghrelin (Andrews et al., 2009; Mani et al., 2014; Zigman et al., 2006) suggesting a common higher order regulation. Few studies have however investigated the role of ghrelin in both dopaminergic structures. The present review aims to provide a comprehensive picture of the role of ghrelin on SNc and VTA dopaminergic neurons both in physiology and in several pathological conditions and to highlight its potential as a biomarker and a disease-modifying compound in PD and anorexia nervosa (AN) in view of the recent literature.

2. Ghrelin: a pleiotropic hormone?

2.1. Origin and biosynthesis of ghrelin

The orexigenic hormone ghrelin has initially been discovered in rat stomach extracts and is implicated in numerous functions as detailed below in §2.3. (Kojima et al., 1999; Méquinion et al., 2013; Müller et al., 2015; Zigman et al., 2016). The gene encoding ghrelin has been identified in numerous species and its sequence is highly conserved among mammals such as humans, rhesus monkeys, rats, mice, cows, pigs, sheep, dogs and gerbils (Angeloni et al., 2004; Tomasetto et al., 2001). The human *GHRL* gene is located on chromosome 3 at position 3p25-26 and codes for a 117 amino acid-long preprohormone, named preproghrelin. This precursor is cleaved into proghrelin, a 94 amino acid-long peptide (Kojima and Kangawa, 2005). In the endoplasmic reticulum, proghrelin will undergo acylation through the action of the enzyme ghrelin-octanoyl-acyltransferase which enables the transfer of an octanoyl group from the octanoyl-coenzyme A to the hydroxyl group of the proghrelin third N-terminal serine (see Fig. 2; Bayliss et al., 2016a; Kojima and Kangawa, 2005; Labarthe et al., 2014; Zhu et al., 2006). Proghrelin is further cleaved by the prohormone convertase 1/3 thus generating a 28 amino acid-long peptide named ghrelin and a 23 amino acid-long peptide named obestatin (Zhu et al., 2006). Ghrelin is released into the bloodstream in two biologically distinct states, acyl- and desacyl-ghrelin, the latter being the major form (Takagi et al., 2013). A large proportion of acyl-ghrelin is indeed rapidly converted to desacyl-ghrelin in the plasma by acyl-protein thioesterase 1 (Satou et al., 2010).

Ghrelin is mainly expressed in the stomach by X/A-like oxyntic gland cells of the gastric fundus mucosa (Kojima et al., 1999; Müller et al., 2015). It is also expressed at lower levels in many other tissues including the intestinal tract, the pancreas, the gall bladder, the liver, the gonads or the breast (Gnanapavan et al., 2002). Ghrelin is however not expressed in the brain. The initial report of ghrelin expression within the hypothalamus (Cowley et al., 2003) was in fact based on non-specific antibody staining as demonstrated later by Furness et al. (2011). Similarly, other authors have not been able to find any preproghrelin mRNA in this brain structure (François et al., 2015). Despite the lack of centrally produced ghrelin and the limited capacity of ghrelin to cross the blood-brain barrier (Banks, 2002; Cabral et al., 2013; Schaeffer et al., 2013) ghrelin receptors have been described in the SNc and VTA (Andrews et al., 2009; Mani et al., 2014; Wellman and Abizaid, 2015; Zigman et al., 2006), suggesting that brain cells expressing ghrelin receptors might respond to ligands other than centrally produced ghrelin. Nevertheless, SNpc and VTA neurons expressing ghrelin receptors readily respond to ghrelin in slice preparations and to direct microinjections (Abizaid et al., 2006).

2.2. Ghrelin receptors

Ghrelin is the only known endogenous ligand of the growth hormone secretagogue receptor (GHSR; Gutierrez et al., 2008; Howard et al., 1996). It was identified in 1996 as an orphan receptor encoded