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Review

The roles of peripheral serotonin in metabolic homeostasis

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ABSTRACT

Metabolic homeostasis in the organism is assured both by the nervous system and by hormones. Among a plethora of hormones regulating metabolism, serotonin presents a number of unique features. Unlike classical hormones serotonin is produced in different anatomical locations. In brain it acts as a neurotransmitter and in the periphery it can act as a hormone, auto- and/or paracrine factor, or intracellular signaling molecule. Serotonin does not cross the blood–brain barrier; therefore the two major pools of this bioamine remain separated. Although 95% of serotonin is produced in the periphery, its functions have been ignored until recently. Here we review the impact of the peripheral serotonin on the regulation of function of the organs involved in glucose and lipid homeostasis.

1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is a bioamine derived from the amino acid tryptophan. In serotonin producing cells, tryptophan is hydroxylated by the rate limiting enzyme tryptophan hydroxylase (TPH) and subsequently decarboxylated by aromatic acid decarboxylase (AADC) [1]. Serotonin was found in a variety of organisms including fungi, plants and invertebrates [2–4]. In vertebrates, two major pools of serotonin can be distinguished: the brain serotonin, synthesized mainly in the brainstem, and the peripheral serotonin. Synthesis of serotonin in both locations relies on the enzyme tryptophan hydroxylase, which is encoded by two different genes, *Tryptophan hydroxylase 1* (*Tph1*) and *Tryptophan hydroxylase 2* (*Tph2*) expressed in the periphery and in the brain, respectively. Serotonin does not cross the blood–brain barrier, and thus each pool of this molecule has its distinct functions [5] (Fig. 1). In the brain serotonin serves as a neurotransmitter. It regulates multiple physiological aspects, including: behavior, learning, and appetite and glucose homeostasis, which have been extensively reviewed [6–8]. However, the brain-derived serotonin accounts only for around 5% of total body serotonin [5]. The remaining 95% of serotonin is produced in the peripheral organs and it became clear in recent years that it regulates function of multiple aspects of physiology.

In the periphery the vast majority of serotonin is produced by enterochromaffin cells of the gut. The Gut-derived serotonin (GDS) can act locally in the gastrointestinal (GI) tract or it can enter into the blood circulation. In the blood, serotonin is taken up and stored by platelets and is released during blood coagulation. Approximately only 2% of the blood serotonin is free in the fluids and can act directly as a hormone [5] (Fig. 2). Interestingly, multiple other peripheral cell types including pancreatic β cells [9,10], adipocytes [11], and osteoclasts [12] can produce serotonin. Thus, serotonin availability in the peripheral tissues is determined by both the local production and by concentration "of the free hormone" in the blood.

Serotonin-mediated signaling in target cells is further complicated by the existence of at least fourteen different receptors for this hormone. Seven classes of serotonin receptors (5-hydroxytryptamine receptors – Htrs) have been identified so far (Htr1 to Htr7). Among them, Htr3 is the only ligand-gated ion channel receptor for serotonin. All other serotonin receptors belong to the G-protein coupled receptor superfamily. However, different classes of Htrs are coupled to a variety of G-proteins and evoke distinct intracellular signaling cascades [5,13] (Fig. 1). Moreover, extracellular serotonin might be taken up by various cell types through serotonin transporters (SERT), subsequently metabolized, and degraded. Importantly, intracellular metabolites of serotonin might also act as signaling molecules [14].

Abbreviations: FFAs, free fatty acids; GDS, gut-derived serotonin; 5-HT, serotonin, 5-hydroxytryptamine; Htr, 5-hydroxytryptamine (serotonin) receptor; Tph1, tryptophan hydroxylase 1

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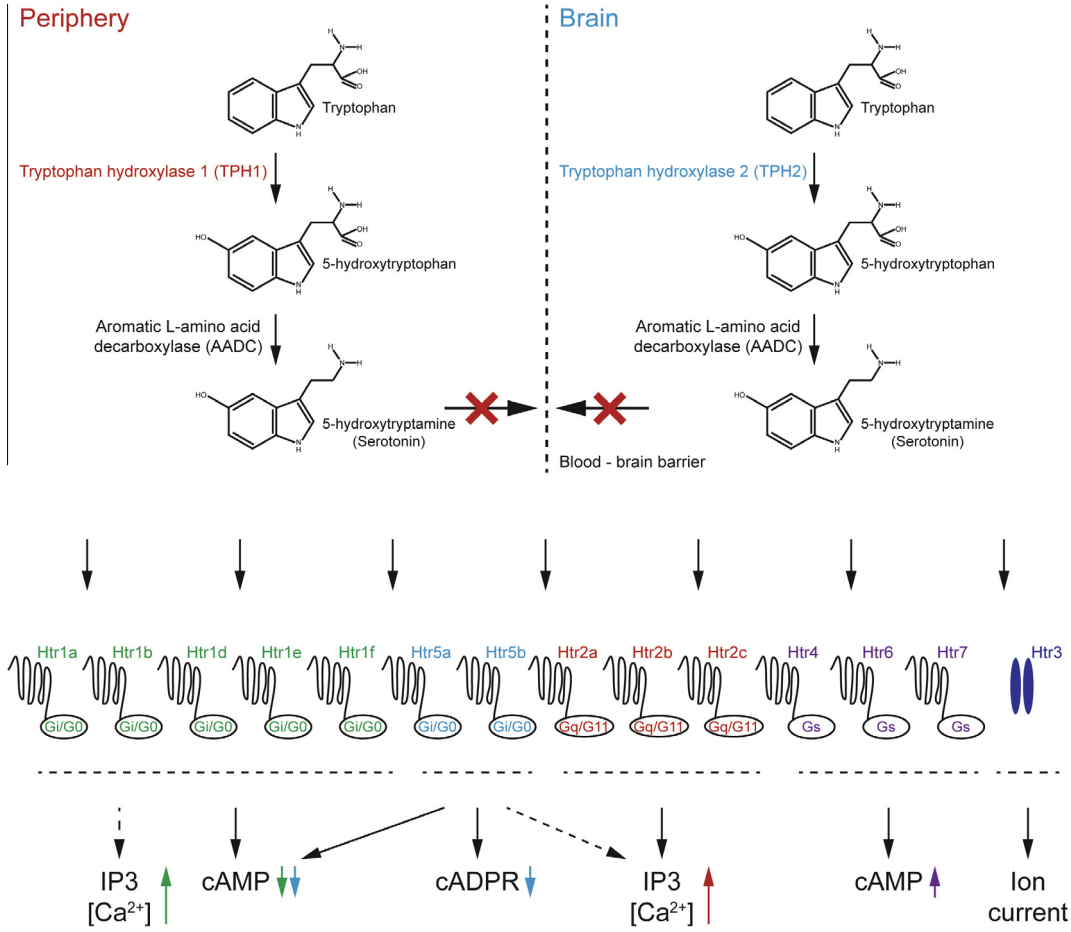

Fig. 1. Serotonin synthesis and signaling in the brain and in periphery. The amino acid tryptophan is hydroxylated by the rate-limiting enzyme tryptophan hydroxylase (TPH) and then subsequently decarboxylated by aromatic acid decarboxylase (AADC). In vertebrates two forms of TPH, encoded by two different genes, can be distinguished: TPH1, which is expressed in the periphery, and TPH2 expressed mainly in the brain. Since serotonin cannot cross the blood–brain barrier this molecule exhibits distinct functions in both locations. Serotonin exerts its effects in target cells through at least fourteen receptors. Thirteen of them belong to the G-protein coupled receptors (GPCR) superfamily. Among these, four subfamilies are distinguished, based on their coupling to different G-proteins and utilization of different secondary messengers. Htr3 is the only ligand-gated ion channel receptor for serotonin. In the figure: cAMP – cyclic adenosine monophosphate, cADPR – cyclic adenosine diphosphate ribose, IP3 – inositol trisphosphate.

In this review, we summarize the different aspects of auto-, para- and endocrine actions of serotonin produced in the periphery on the regulation of glucose and lipid homeostasis.

2. Serotonin regulates pancreatic β cell function in an autocrine manner

Insulin producing pancreatic β cells are the main cell type regulating glucose and lipid homeostasis in the body. Generally, insulin promotes glucose uptake in the peripheral cells, synthesis of glycogen and proteins, as well as de novo lipogenesis. At the same time insulin suppresses hepatic glucose production (gluconeogenesis) and the release of triglycerides stored in adipose tissue (lipolysis). Since insulin regulates key aspects of nutrient homeostasis, its production and secretion from pancreatic β cells need to be tightly regulated to meet different physiological and environmental challenges. Therefore, insulin production, secretion, and pancreatic β cells mass are controlled not only by nutrients (mainly glucose) levels but also by the nervous system and hormones [15,16].

Pancreatic β cells share common developmental features with serotonin producing neurons in the hindbrain [17]. Indeed, a number of studies confirmed that enzymes required for serotonin synthesis and secretion are also expressed in β cells. Interestingly, β cells express both brain- and peripheral-specific rate-limiting enzymes for serotonin synthesis (Tph1 and Tph2) [9,10,17–19]. Therefore, both locally produced serotonin and serotonin present in the circulation might influence the function of pancreatic β cells.

Tph1-deficient mice (*Tph1*−/−) are glucose intolerant and develop mild form of diabetes [10,20] due to impaired insulin secretion from β cells [10]. Paulmann and colleagues demonstrated that the intracellular concentration of serotonin correlates positively with insulin secretion rate. Their experiments performed on the rat insulinoma cell line INS1 suggest also that extracellular serotonin might suppress insulin secretion [10]. Accordingly, isolated Tph1-deficient β cells display impairment in insulin granule exocytosis. The same study showed that intracellular serotonin covalently couples specific small GTPases (Rab3a and Rab27a) to activate them, which in turn promotes glucose-mediated insulin granule exocytosis. Under normal conditions, pancreatic islet morphology, number and size are unaffected in *Tph1*−/− mice [10]. Taken together this study suggests that serotonin promotes insulin granule exocytosis in β cells in an autocrine, receptor independent manner. Of note, reduction of serotonin levels exclusively in the circulation (by deleting *Tph1* in the enterochromaffin cells of the gut) does not influence insulin levels in mice [20]. Accordingly, pancreatic β cell-specific deletion of Tph1 resulted in decreased insulin secretion, circulating insulin levels and impaired tolerance to glucose in diabetic mice [21]. The same authors showed that deletion of ligand-gated ion channel serotonin receptor Htr3a in

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