Critical Review

The Cardiovascular Actions of DOPA Mediated by the Gene Product of *ocular albinism 1*

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Abstract. L-3,4-Dihydroxyphenylalanine (DOPA) is the metabolic precursor of dopamine, and the single most effective agent in the treatment of Parkinson's disease. One problem with DOPA therapy for Parkinson's disease is its cardiovascular side effects including hypotension and syncope, the underlying mechanisms of which are largely unknown. We proposed that DOPA is a neurotransmitter in the central nervous system, but specific receptors for DOPA had not been identified. Recently, the gene product of *ocular albinism 1* (OA1) was shown to possess DOPA-binding activity. It was unknown, however, whether or not OA1 is responsible for the actions of DOPA itself. Immunohistochemical examination revealed that OA1 was expressed in the nucleus tractus solitarii (NTS). OA1-positive cells adjacent to tyrosine hydroxylase–positive cell bodies and nerve fibers were detected in the depressor sites of the NTS. OA1 knockdown using *oa1*-specific shRNA-adenovirus vectors in the NTS reduced the expression levels of OA1 in the NTS. The prior injection of the shRNA against OA1 suppressed the depressor and bradycardic responses to DOPA but not to glutamate in the NTS of anesthetized rats. Thus OA-1 is a functional receptor of DOPA in the NTS, which warrants reexamination of the mechanisms for the therapeutic and untoward actions of DOPA.

Keywords: DOPA, neurotransmitter, nucleus tractus solitarii, GPCR, baroreceptor reflex

Introduction

Searching for endogenous active substances and their receptors has been one of the most important issues to be addressed in the field of pharmacological sciences. L-3,4-Dihydroxyphenylalanine (DOPA), a precursor of dopamine, is the most suitable drug in theory for supplementing dopamine deficiency in the brain of Parkinson's disease and has been believed to be an inert amino acid (1 – 3). Contrary to this generally accepted idea, we have proposed that DOPA also plays a role as a neurotransmitter (4, 5). DOPA is released upon nerve excitation in a transmitter-like manner under in vitro and in vivo experimental conditions (5, 6). There are neurons that are positive for tyrosine hydroxylase (TH) but

aromatic L-amino acid decarboxylase (AADC)-negative, and DOPA-positive but dopamine-negative (7 – 9). Autoradiographic studies using [^{3}H]-DOPA revealed a sodium ion-dependent DOPA uptake system in the central nervous system (CNS) (10). DOPA produces various presynaptic and postsynaptic responses even under essentially complete inhibition of AADC, and these actions are distinct from those of dopamine (11 – 13). The actions of DOPA are antagonized by DOPA methyl ester (DOPA ME) or DOPA cyclohexyl ester (DOPA CHE) in a competitive fashion (7, 14). A most prominent effect of DOPA is its depressor and bradycardic actions in the nucleus tractus solitarii (NTS) in anesthetized rats (7, 12). Thus DOPA fulfills the classically defined criteria for neurotransmitter (4). However, the receptor(s) for DOPA had not been identified (4, 5). Recently, it was shown that the protein ocular albinism 1 (OA1), one of the orphan G protein–coupled receptors (GPCRs) also known as GPR143 (15), possesses DOPA-binding activity (16). OA1 is the pro-

tein product of the *oa1* gene (17). Mutations of the *oa1* gene cause ocular albinism type 1, an X-linked disorder characterized by severe reduction of visual acuity, retinal hypopigmentation, foveal hypoplasia, optic misrouting, and the presence of giant melanosomes in skin melanocytes and retinal pigment epithelium (18, 19). Recent findings provide evidence that OA1 is a receptor that mediates depressor and bradycardic responses to DOPA in the NTS (21), thereby indicating that OA1 is a functional receptor for DOPA. In this review, we characterize OA1 as a receptor for DOPA and discuss the cardiovascular effects of DOPA from the standpoint of the DOPA–OA1 signaling system.

The effects of DOPA on cardiovascular functions

AADC is expressed in neuronal cells, where it participates in the synthesis of neurotransmitters, and in non-neuronal cells, including liver, kidney, lung, spleen, and endothelial cells, where its function is less clearly understood (22). Orally administered DOPA is metabolized in the peripheral tissues and in the gastrointestinal tract by AADC, catechol-*O*-methyltransferase and monoamine oxidase A. This metabolism substantially reduces the effective dose of DOPA available to the brain and substantially increases the adverse peripheral effects of DOPA such as nausea, vomiting, tachycardia, hypotension, and other cardiovascular effects. When DOPA is administered in combination with peripheral AADC inhibitor, for example, carbidopa, a greater fraction of the DOPA is available to the brain. Therefore, a smaller dose of DOPA is required for clinical efficacy, and the drug has less severe adverse effects in the periphery. Although some controversial findings such as hypotensive and hypertensive effects of peripherally administered DOPA have been reported (22 – 25), most of these side effects are mainly due to dopamine and other catecholamines converted from DOPA by AADC. In fact, DOPA after being taken up into catecholaminergic neurons can be converted to dopamine and other catecholamines, which are released from catecholaminergic neurons or induce non-vesicular release by displacing noradrenaline at the sympathetic nerve terminals (tyramine-like effect). Dopamine converted from DOPA in non-neuronal tissues also could exert its cardiovascular and/or renal actions via β-adrenergic receptors and dopamine D_1- or D_2-receptor. Activation of D_1 receptors on vascular smooth muscle is associated with vasodilatation, primarily in the renal, mesenteric, cerebral, and coronary circulations (26). In the kidney, D_1 receptors have also been localized at both the luminal and basolateral membranes of proximal tubules (27). Stimulation of these receptors leads to natriuresis and diuresis via acti-

vation of enzymes involved in second messenger systems, i.e., adenylate cyclase and phospholipase C. Renal D_2 receptors are found in intra-renal arteries and arterioles, the adventitia-media, the intima, and tubules. Presynaptic D_2 receptors on sympathetic nerve terminals decrease the release of noradrenaline (28). In addition to its effects on renal blood flow, glomerular filtration rate, urinary sodium, and water excretion, dopamine also promotes phosphate excretion and antagonizes the hydro-osmotic effect of vasopressin. The idea that these actions of DOPA is mediated by its conversion to dopamine is supported by the findings that almost all these effects of DOPA are markedly suppressed or abolished by the treatment of AADC inhibitors (2).

Although a large amount of work suggests that DOPA is largely inert, there are some reports showing that the cardiovascular effects of DOPA are seen under the treatment of peripheral AADC inhibitors (23, 24, 29). For example, intravenous administration of DOPA after blockade of extracerebral AADC by carbidopa produces decreases in plasma renin activity and blood pressure (29). DOPA reduces sympathetic nerve activity and blood pressure in spontaneously hypertensive rats after peripheral AADC inhibition (24). It might be possible that these effects are caused by the actions of DOPA itself in peripheral tissues. Under these experimental conditions, however, central AADC may be intact, thereby leaving open the possibility that these actions of DOPA are caused by its conversion to dopamine in the CNS.

DOPAergic relay in the lower brainstem

Although most of the pharmacological actions of DOPA are attenuated or abolished by AADC inhibition, many investigators have studied whether DOPA can induce any cellular responses by itself. DOPA shows predominantly excitant action in cat cortical neurons (30). DOPA also produces excitatory actions in isolated hemisected spinal cord of the frog (31). However, the concentrations of DOPA required were of milli-molar ranges, and the potency of the excitatory actions is lower than that of L-glutamate (glutamate) and other related compounds in these experiments (30, 31). Consistently, milli- or submillimolar concentrations of DOPA are capable of inducing a current response in *Xenopus laevis* oocytes expressing AMPA-receptor subunits GluA1–A4. DOPA inhibits the specific binding of [^{3}H]-AMPA in the sub-millimolar range in rat brain membrane preparations (32). The physiological relevance of such DOPA–AMPA receptor interactions remains unknown.

The first evidence for a neurotransmitter role of DOPA was obtained in the lower brain stem (7, 12). The barore-

ceptor reflex is the principal neural mechanism by which the cardiovascular system is regulated under negative feedback control in the lower brain stem. Arterial baroreceptors are located both in the aortic arch and carotid sinus. The primary baroreceptor afferents terminate in the NTS to carry reflex information. One of the most plausible neurotransmitter candidates is glutamate. Indeed, glutamate microinjected into the NTS induces depressor and bradycardic responses in anesthetized rats (4, 12, 33). Although recent reports suggest that NMDA and metabotropic glutamate receptors are also involved, non-NMDA receptors are probably the primary mediators of the aortic baroreflex (34). On the other hand, it was reported that there exist neurons that may contain DOPA as an end product, i.e., DOPA-positive and dopamine-negative or TH-positive and AADC-negative neurons in the NTS (8, 9, 21). If DOPA plays roles as a neurotransmitter (5), it can induce some actions in the NTS (12). DOPA, but not dopamine, microinjected into the NTS produces depressor and bradycardic responses in anesthetized rats pretreated with 3-hydroxybenzylhydrazine (i.p.), a central AADC inhibitor (12). Furthermore, phenylephrine, a selective α_1-adrenergic receptor agonist induces hypertension, which triggers the release of DOPA in the NTS and induces reflex bradycardia temporally associated with the rise and recovery of blood pressure (7). The DOPA release and bradycardia are abolished by denervation of bilateral carotid sinus and aortic nerves, which contain the baroreceptor afferents, while similar changes of blood pressure are seen. This finding suggests that reflex information is carried from baroreceptors to the NTS via the sino-aortic nerves and releases DOPA in the NTS. The DOPA released from the sino-aortic nerve terminals in the NTS area may result in bradycardia via reflex, increase in the peripheral vagal tone, and/or decrease in the sympathetic tone in the heart. There is also a tonically functioning DOPA system to mediate cardiodepressor and cardiopressor control in the caudal ventrolateral medulla (CVLM) and rostral ventrolateral medulla (RVLM), respectively (4, 35, 36). DOPA microinjected into depressor sites of the unilateral CVLM produces dose-dependent hypotension and bradycardia. DOPA ME unilaterally microinjected completely antagonizes cardiodepressor responses to DOPA (36). Likewise, DOPA microinjected into pressor sites of the unilateral RVLM dose-dependently induces hypertension and tachycardia, which are antagonized by DOPA ME microinjected unilaterally (35). Electrical lesion of the right NTS produces a selective decrease of 40% of the DOPA contents in the ipsilateral CVLM (4). These findings suggest that a DOPAergic and monosynaptic relay projects from the NTS directly to depressor sites and/or indirectly to some
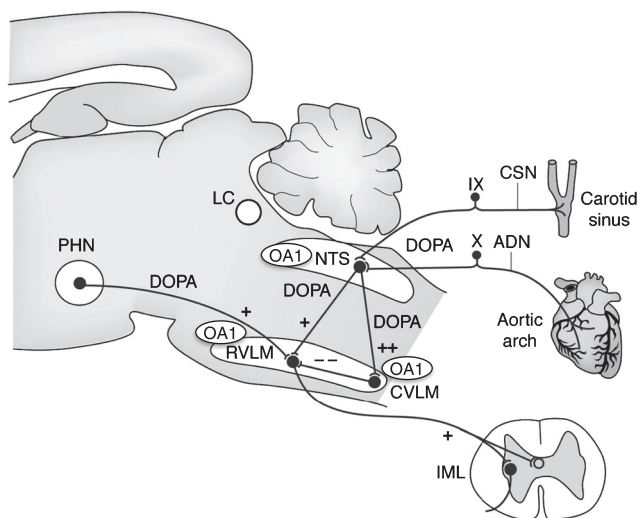

Fig. 1. Central regulation via baroreceptor reflex in the lower brain stem. The baroreflex is the principal neuronal mechanism by which the cardiovascular system is regulated under negative feedback control. Baroreceptors are located in the aortic arch and the carotid sinus. The primary baroreceptor afferents (the aortic depressor nerve (ADN) and the carotid sinus nerve (CSN)) terminate in depressor sites of the NTS (7). The NTS neurons send excitatory projections to the caudal ventrolateral medulla (CVLM) and the rostral ventrolateral medulla (RVLM). The tonicity of the excitatory NTS–RVLM pathway, shown as '+', appears to be less than the tonicity of the predominant excitatory NTS–CVLM pathway, shown as '++'. Vasomotor tone is reduced by the neuronal activity of the CVLM, the integration of which constitutes the central pathway for the baroreflex. GABA-containing neurons in the CVLM project directly to the RVLM to inhibit excitatory activity. The excitatory neurons of the RVLM project directly to the intermediolateral cell column (IML) of the thoraco-lumbar spinal cord, the main origin of the sympathetic outflow. OA1 is expressed in the NTS, RVLM, and CVLM. Abbreviation: LC, locus caeruleus. Modified from (37).

neurons near depressor sites in the CVLM. On the other hand, a 20% decrease in the contents of DOPA is seen after lesion of the NTS in the ipsilateral RVLM. This is consistent with the idea that the excitatory effect of the pathway from the NTS to the RVLM is masked by the predominant effect of the pathway from the NTS to CVLM and then to the RVLM mediating depressor responses (37) (Fig. 1). Thus the depressor or pressor actions of systemically administered DOPA may be determined by the total balance among the actions of DOPA in these cardiovascular centers.

Although glutamate probably plays a role in mediating the baroreceptor reflex in the NTS, it seems unlikely that DOPA induces the cardiovascular responses by mechanisms in which transmitter glutamate is primarily involved. Binding experiments using radiolabelled glutamatergic ligands show that DOPA ME and DOPA CHE, competitive antagonists for DOPA (14),

do not interact with non-NMDA receptors, but interact with the specific binding sites of $[^3H]$-MK-801 with IC_{50} of 1 mM and 0.68 mM, respectively. In addition, DOPA ME or DOPA CHE suppresses the depressor and bradycardic response to DOPA microinjected into the NTS, which argues against the idea that the DOPA produces these actions through non-NMDA receptors.

DOPA-induced cardiovascular response mediated by OA1 in the NTS

These findings suggest the cardiovascular actions of DOPA are mediated by specific receptor(s) for DOPA, other than glutamatergic receptors. Recently, OA1, one of an orphan GPCRs also known as GPR143, was shown to possess DOPA-binding activity and could function as a DOPA receptor in retinal pigment epithelium cells (16). OA1 is the protein product of the *oa1* gene (17), and mutation of the *oa1* gene causes ocular albinism type 1, an X-linked disorder characterized by severe reduction of visual acuity, retinal hypopigmentation, foveal hypoplasia, optic misrouting, and retinal pigment epithelium (18, 19). However, whether OA1 mediates the cardiovascular actions of DOPA (5, 37) remained an open question.

If OA1 mediates the actions of DOPA, OA1 should be expressed in the depressor sites of the NTS. To localize OA1, immunohistochemical examination using an anti-OA1 antibody was performed in the rat brain (21). OA1 was expressed in the medial NTS (Fig. 2). In the NTS, some cells are labeled immunocytochemically with TH, a DOPA-forming enzyme (7). To examine the relationships between OA1-positive and TH-positive neurons, immunohistochemical examination with anti-TH antibody was performed. As with the OA1-immunoreactive cells, TH-immunoreactive neurons were observed in the medial NTS. These findings are consistent with previous findings that DOPA-uptake cells or DOPA-positive and AADC-negative neurons are localized in the NTS (4, 7). Consistently, there were TH-positive cells that lack immunoreactivity to AADC in the dorsal motor nucleus of the vagus (Fig. 3) (20). The specificity of the antibody was confirmed by a knock-down experiment on OA1 in the NTS of adult rats. Quantitative RT-PCR and immunohistochemical examination revealed that injection of adenovirus carrying the relevant shRNA sequences against OA1 into the NTS decreased the expression of OA1 mRNA and the levels of OA1 immunofluorescence signals in the NTS, respectively
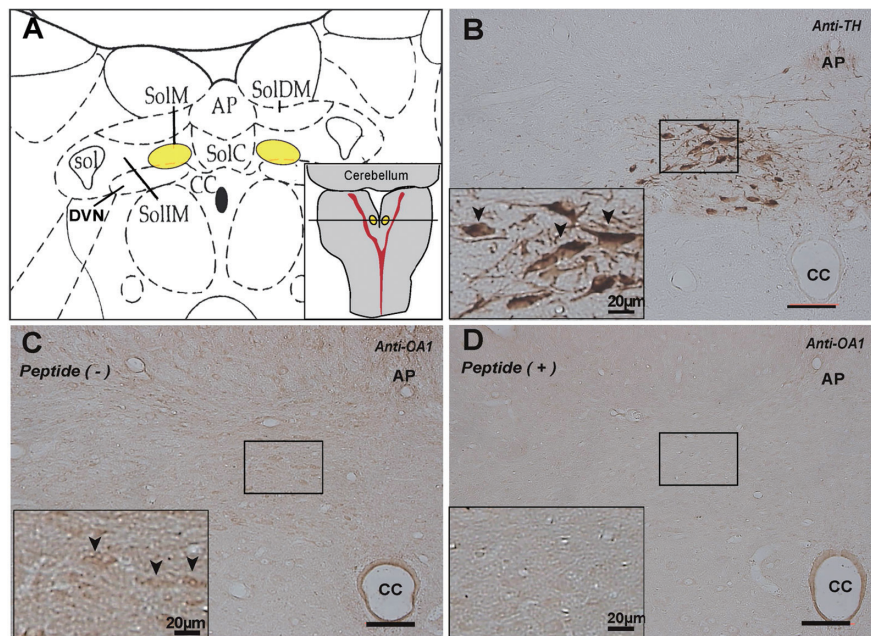

Fig. 2. OA expression in the NTS. A) Diagram of rat medulla oblongata in a coronal section. Image of boxed area in (A) corresponds to the images shown in (B) and (C). CC: central canal, AP: area postrema, SolM: nucleus of solitary tract medial, SolC: commissural, sol: solitary tract. (B) The coronal section of rat medulla oblongata was immunostained with anti-TH antibody. Arrowheads in a magnified image (left lower panel) of the boxed area indicate the cells positively stained with anti-TH antibody. C) The coronal section of rat medulla oblongata immunostained with anti-OA1 antibody. Arrowheads in a magnified image (left lower panel) of the boxed area indicate the cells positively stained with anti-OA1 antibody in the absence [C, peptide (−)] of the peptide antigen. The signals were suppressed by the presence of the peptide [D, peptide (+)]. Scale bar = 100 μm. A magnified image, scale bar = 20 μm. Modified from (21).
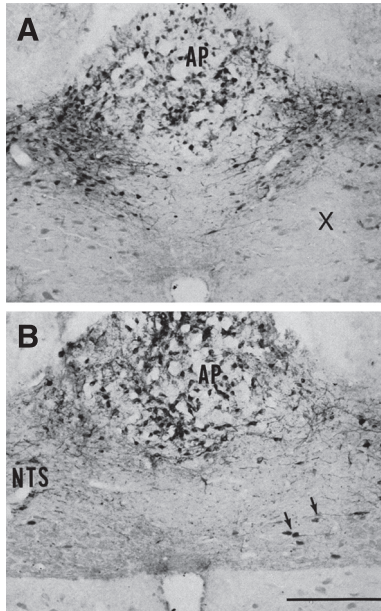
Fig. 3. TH and AADC expression in the NTS. Localization of the cells in the NTS by AADC (A) and TH (B) immunostaining on adjacent sections. In (A), there are dense clusters of AADC-positive cells in the dorsolateral NTS lateral to area postrema (AP), where only few TH-positive cells are observed in this area. TH-positive cells (arrows) in the dorsal motor nucleus of the vagus (X) are AADC-negative. Scale bar = 250 μm. Modified from (20).

(21). These findings further indicate that the anti-OA1 antibody is specific for OA1 and that OA1 is expressed in the NTS. Furthermore, introducing the shRNA against OA1 into the NTS essentially abolishes the depressor and bradycardic responses to DOPA, without modifying the responses to glutamate. This finding clearly indicates that OA1 in the NTS mediated depressor and bradycardic responses to DOPA, but not to glutamate (Fig. 4) (21). We recently found that OA1 is also expressed in the RVLM and CVLM (39), further suggesting the idea that OA1 is a functional receptor for DOPA in the lower brain stem (Fig. 1).

DOPA CHE behaves as an antagonist of DOPA in OA1-expressing cells

To further demonstrate that OA1 is the functional receptor for DOPA, the binding activity of DOPA CHE against OA1 was tested. Previous studies indicated that DOPA ME and DOPA CHE could act as competitive antagonists against DOPA-induced facilitation of impulse-evoked noradrenaline release from rat hypothalamic slices (40) and against DOPA-induced depressor and bradycardic actions in the NTS of anesthetized rats (14). For example, DOPA CHE (30 – 100 ng) microinjected in the NTS dose-dependently shifts the dose–response-curve for L-DOPA (18 – 300 ng) to the right, with DOPA CHE (100 ng) inducing a slight reduction of the
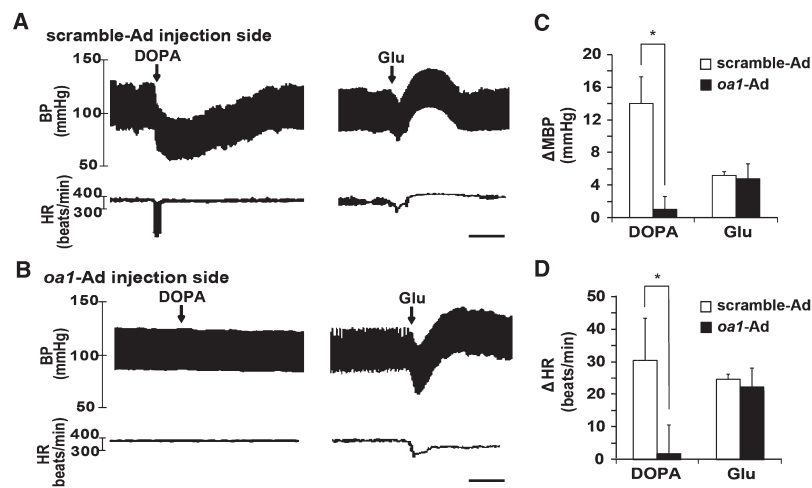

Fig. 4. Introducing *oa1*-specific shRNA into the NTS attenuates the depressor and bradycardic responses to DOPA. A, B) Typical traces of the effects of DOPA and glutamate (Glu) microinjected into the right or left NTS infected with scramble-(scramble-Ad) or *oa1*-specific shRNA adenovirus (*oa1*-Ad) vectors on blood pressure (BP) and heart rate (HR) in anaesthetized rats. In the scramble side, the depressor and bradycardic responses to DOPA were detected, whereas these responses were suppressed in the side injected with OA1 shRNA-adenovirus. Responses to Glu were detected in the OA1 shRNA-adenovirus injected side as well as in the scramble-adenovirus–injected side. Scale bar, 1 min. C, D) Summarized effects of scramble- and OA1 shRNA vectors on the depressor (*Δ*MBP) and bradycardic (*Δ*HR) responses to DOPA and Glu. *$P < 0.05$, compared with the levels of the scramble side (n = 5). Modified from (21).

maximum response (14). In COS cells expressing OA1, DOPA CHE displaced the specific [^{3}H]-DOPA binding, confirming that DOPA CHE is a ligand for OA1. DOPA reproducibly and reliably induced the [Ca^{2+}]i response in a cell line expressing OA1. The DOPA-induced response was not observed in the cell line not expressing OA1. DOPA CHE antagonized the DOPA-induced [Ca^{2+}]i response. These findings provide convincing evidence that DOPA induces the [Ca^{2+}]i response via OA1 and that DOPA CHE acts as a competitive antagonist against OA1 as previously assessed by in vivo measurement of the cardiovascular responses to DOPA (14).

As shown by Lopez et al., the specific binding of [^{3}H]-DOPA was detected in CHO cells expressing OA1 with a K_d value of 79.1 μM, as assessed by Scatchard plot analysis. DOPA CHE displaced the [^{3}H]-DOPA binding with a K_i value of 135.9 μM. This finding indicates that the [^{3}H]-DOPA binding to OA1 expressed in CHO cells was of low affinity. Some receptors with a relatively low affinity have been reported (41). However, this might not reflect the nature of OA1 in native cells because the possibility of a low expression of OA1 or other factors in such cell lines cannot be excluded. Indeed, nanomolar concentrations of DOPA can induce presynaptic regulation of impulse-evoked catecholamine release from brain slices (11, 42). In in vivo experiments, DOPA at doses comparable to those of glutamate induces depressor and bradycardic response in the NTS of anesthetized rats (7, 12). It might be possible that some interacting proteins or receptors with OA1 are necessary for high affinity binding of DOPA to OA1. OA1 could also form functional homo- and/or hetero-oligomers. For example, GABA$_B$ receptors are formed from the heterodimerization of two similar seven-transmembrane subunits termed GABA$_{B1}$ and GABA$_{B2}$. The two subunits interact by direct allosteric coupling such that GABA$_{B2}$ facilitates the coupling of GABA$_{B2}$ to G proteins (43, 44). Like GABA$_B$ receptors, heterodimerization might be important for OA1 function.

Concluding remarks

OA1 is a functional receptor for DOPA in mediating cardiovascular responses to DOPA in the NTS. The pharmacological effects of DOPA are mediated not only through its conversion to dopamine, but also the activities by itself mediated by OA1. Our finding could provide a new perspective for DOPA therapy. Delineating physiological functions of OA1 and searching for its specific ligands may be the most important tasks ahead.

Conflicts of Interest

The authors have no conflicts of interest to report.

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