Cannabinoid receptor 1 signaling in cardiovascular regulating nuclei in the brainstem: A review

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ABSTRACT

Cannabinoids elicit complex hemodynamic responses in experimental animals that involve both peripheral and central sites. Centrally administered cannabinoids have been shown to predominantly cause pressor response. However, very little is known about the mechanism of the cannabinoid receptor 1 (CB1_R)-centrally evoked pressor response. In this review, we provided an overview of the contemporary knowledge regarding the cannabinoids centrally elicited cardiovascular responses and the possible underlying signaling mechanisms. The current review focuses on the rostral ventrolateral medulla (RVLM) as the primary brainstem nucleus implicated in CB1_R-evoked pressor response.

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Cannabinoids

Cannabinoids are heterogeneous group of compounds that target cannabinoid receptors: CB1 and CB2. These compounds include the naturally occurring Δ9-tetra-hydrocannabinol (Δ9-THC), isolated from the plant Cannabis sativa (marijuana), endogenous compounds known as endocannabinoids (ECs), as well as other synthetic compounds. Since at least 2000 B.C., the plant Cannabis has been long used for recreational and medical purposes. Δ9-THC, Cannabidiol (CBD), and cannabinol are the most abundant natural cannabinoids active at CB1 and CB2 receptors, but only Δ9-THC has an equal affinity for both CB1 and CB2 receptors [1,2]. The first endogenous ligand for both cannabinoid receptors [2], anandamide, is a derivative of arachidonic acid (arachidonoyl ethanolamide; AEA), which was isolated from pig brain in 1992 [3], and 2-arachidonoyl glycerol (2-AG) is another abundant ECs [4].

Most of the endogenous cannabinoids discovered so far are agonists except the inverse agonist virodhamine [5]. The high affinity non-eicosanoid cannabinoids CP55940 and the amino-alkyl-indole cannabinoid WIN55,212-2 were developed by Pfizer and Sterling Winthrop, respectively. SR141716A and AM251 are selective antagonists for the CB1_R, while SR144528 is selective for the CB2_R [2,6]. Notably, most of the synthetic compounds are highly lipophilic and water insoluble except for O-1057, which is highly water soluble and possesses comparable potency as CP55940 [7]. Hemopressin, a
short peptide identified in rat brain, has been recently categorized as inverse cannabinoid agonist [8,9].

**Cannabinoid receptor 1**

It is now known that cannabinoids exert their actions mainly via two subtypes of G-protein-coupled receptors (GPCRs): CB1 and CB2. Additional non-CB1, non-CB2 established GPCRs, such as GPR55 and GPR18, are also targeted by these compounds (e.g. anandamide, virodhamine, CP559440, and AM251 but not WIN55,212-2) [10–14]. Our review focuses on the CB1 receptor, which is found primarily in the CNS, including the cardiovascular regulatory nuclei in the brainstem. The CB1 receptor, a 473-amino-acid protein, was first cloned from a rat cerebral cortex cDNA library [15] and a human brainstem library [16], which maintains the essential topographical features for a G-protein-coupled receptor (GPCR) of (i) seven hydrophobic transmembrane domain regions that extend through the plasma membrane; (ii) three extracellular loops; (iii) three intracellular loops; (iv) an extracellular N-terminal; (v) and an intracellular C-terminal [17].

**CB1R signaling**

Activation of CB1R triggers several downstream effectors including inhibition of adenylyl cyclase, stimulation of inwardly rectifying potassium channels, inhibition of N- and P/Q-type voltage-dependent calcium channels, and activation of mitogen-activated protein kinase (MAPK) pathway. Cannabinoids acting via CB1R reduce cAMP production by inhibiting adenylyl cyclase [18–20] which is antagonized by cannabinoid antagonists SR141716A and LY334515 [21]. These effects are mediated via inhibitory G-protein (G~a~i/o) because they were blocked by Giαi/o-selective pertussis toxin in mammalian brain and in cultured neuronal cells [18–20]. Many other CB1R-mediated physiological functions are G-protein Gxi/o mediated [19,22,23]. However, the diverse, sometimes opposing, CB1R-evoked physiological functions that are not completely attributable to simply lowering intracellular cAMP levels, have led to investigations of the role of other non-Gxi/o signaling mechanisms [24]. In this line, recent studies have linked CB1R coupling to activation of Gαq11 or Gzα. It is possible that heterodimerization between the CB1R and other receptor(s) contribute, at least partly, to this divergent signal transduction. This notion is supported by the reported interaction between CB1R and other co-localized receptors e.g. dopamine D2R, which resulted in accumulation of cAMP [25,26]. Second, CB1R behaves as a Gαq11-G-protein-coupled receptor in cultured hippocampal neurons and trabecular meshwork cells [24,27]. Further, the findings that heterodimerization between CB1R and OX1R resulted in enhanced Gαq11-dependent OX1R signaling in presence of CB1R [28].

**Retrograde CB1R-mediated signaling**

CB1R is located mostly presynaptically, thus playing crucial roles in controlling the release of neurotransmitters at both excitatory and inhibitory synapses. Upon depolarization, the postsynaptically released endocannabinoids activate presynaptic CB1R, which in turn modulates the release of various neurotransmitters [23,29]. For example, WIN55,212-2 inhibited GABA release from presynaptic terminals in cultured hippocampal or ventromedial medulla (RVM) neurons following postsynaptic depolarization [30,31]. The latter effect was completely abolished in presence of selective CB1 receptor antagonists. This phenomenon is termed depolarization-induced suppression of inhibition (DSI). Findings from cerebellar Purkinje cells support the possibility that postsynaptically released endocannabinoids act as retrograde secondary messengers at both inhibitory as well as excitatory synapses because following depolarization, the released endocannabinoids, which stimulate presynaptic CB1R, ultimately suppress presynaptic calcium-induced glutamate release [32]. The latter phenomenon is termed depolarization-induced suppression of excitation or (DSE). Both CB1R mediated DSE and DSI are considered key mechanisms for many of the central effects of endogenous and exogenous cannabinoids.

**Cardiovascular effects of cannabinoids**

The cardiovascular responses to cannabinoids are complex and are dependent on the state of the studied animals (conscious vs. anaesthetized) and the route of administration (systemic vs. central) [33–38].

**Systemic CB1R-evoked cardiovascular effects**

In anesthetized animals, systemically administered cannabinoids elicit predominantly hypotension and bradycardia. These effects are mediated peripherally through prejunctional inhibition of sympathetic outflow and vagal stimulation resulting in reduction in BP and HR, respectively [39–42]. Systemic administration of THC, anandamide, or WIN55,212-2 elicited tri-phasic effects on BP in anesthetized rats: (i) an initial brief hypotensive phase, secondary to a bradycardic response, which was blocked by atropine pretreatment or vagotomy; (ii) a transient pressor response due to direct vasoconstriction; (iii) a more predominant depressor phase. The prolonged depressor phase was mediated via peripheral sympathoinhibition because it was attenuated by cervical spinal transection and blockade of α-adrenoceptors [39–43]. Interestingly, recent studies have suggested that, in addition to the direct vasoconstrictor action discussed above, the transient pressor response evoked by systemic cannabinoids in anaesthetized animals might involve central mechanisms [44,45]. However, the cardiovascular responses of systemically administered cannabinoids in conscious animals are quite different. The prolonged depressor response (phase III) is absent following systemically injected anandamide or WIN55,212-2 which, in contrast, cause predominant pressor responses along with bradycardia in conscious rats [36,37]. The elicited pressor response by systemic WIN55,212-2 in conscious animals is centrally mediated because it was attenuated by ganglion blockade [37]. Importantly, in humans, acute administration of cannabinoid is associated with tachycardia and a pressor response [46–48].

**Central CB1R-evoked cardiovascular effects**

Centrally administered cannabinoids predominantly elicit sympathoexcitation/pressor responses. Studies have elucidated the
involvement of various brainstem nuclei in the cardiovascular responses elicited by central CB1R activation, e.g. Nucleus Tractus Solitarii (NTS) and the rostral ventrolateral medulla (RVLM) [39,49–52].

The NTS

The NTS is located in the brainstem flanked on each side of the fourth ventricle and consists of groups of cells in a column-like structure dorsal to the RVLM and represents the first relay station in the baroreflex arc. Upon stimulation, the NTS elicits a reduction in the BP, HR, and sympathetic outflow [53,54]. The most cardiovascular-relevant part of the NTS is located at the most caudal part of the NTS, which contains synapses from chemo and aortic baroreceptor processes that contact with secondary order neurons within the NTS [55,56]. The latter communicate either directly or indirectly through third order neurons with other nuclei including RVLM, hypothalamus or CVLM [57–60]. Functionally, activation of cardiovascular afferents (chemo or baroreceptors) enhances the release of excitatory amino-acid L-glutamate within the NTS [54], which prompts the excitation of NTS-projections to other baroreflex arc nuclei e.g. RVLM and CVLM. Several reports have shown important roles for activation of CB1R in the NTS in blood pressure regulation [50–52,61]. For examples, activation of NTS cannabinoïd receptors by anandamide enhanced baroreflex-mediated sympathoinhibition, at least partly, via presynaptic inhibition of GABA release [52,62].

The RVLM

In this review, attention has been focused on the RVLM, which plays pivotal role in central control of cardiovascular function [63–65]. The RVLM is the final supraspinal site within the central nervous system that integrates multitudes of influences on blood pressure (BP) from higher brain regions such as paraventricular nucleus, lateral hypothalamus, and periaqueductal gray [64,66]. The RVLM is of high significance in controlling BP since bilateral lesioning of the RVLM leads to a profound fall in BP [59]. The RVLM is located in the ventral part of the brainstem, lateral to the inferior olive, caudal to the facial nucleus, and ventral to the nucleus ambiguous [59,67]. It is heterogeneous in composition and contains multiple cell groups that are different in their neurochemical phenotype (e.g. rostroventrolateralis, gigantocellular nucleus, and paragigantocellularis lateralis [68–71]). Within the RVLM, the adrenergic group C1 neurons, alternatively known as adrenergic neurons, are defined based on their expression of phenylethanolamine-n-methyltransferase (PNMT) [72,73]. The rostral C1 subgroup contains barosensitive neurons which project to the spinal cord [74,75] and provides tonic excitatory inputs to the sympathetic preganglionic neurons [76,77]. Beside catecholamine-containing neurons in RVLM [78], a wide variety of neurotransmitters and receptors are present in the RVLM including substance P [79], neuropeptide Y [80], enkephalin [80,81], adenosine receptors (A2A) [82], P2X receptors [83], Angiotensin II AT1 receptors [84], imidazoline I1 receptors [85,86], α2A adrenergic receptors [87,88], cannabinoid CB1 receptors [89,90], CB2 receptors [91], and mu-opioid receptors [92,93]. The RVLM is a crucial brainstem nucleus for the tonic generation of sympathetic nerve activity [59,60]. Activation of specific neurons within the RVLM causes an increase in BP by increasing peripheral resistance and cardiac output via released catecholamines [94–97]. In addition to cardiovascular control, specific neurons within the RVLM are involved in nociception [98,99] and breathing [100]. Intracisternal (i.c) administration [101–103] or intra-RVLM microinjection [90,104] of cannabinoids such as WIN55,212-2 or CP-55940 elicited a pressor response and caused increases in sympathetic nerve activity, plasma norepinephrine and blood pressure, in conscious and anesthetized animals, and these responses were attenuated by pretreatment with the CB1R antagonists SR171416A or AM251. The significant increase in tyrosine hydroxylase immunoreactive neurons (TH-ir) expressing c-Fos, a marker of neuronal activity, following i.c. WIN55,212-2 provided direct in vivo evidence that central CB1R-evoked pressor response involves activation of RVLM-catecholaminergic neurons [102], which was abrogated by CB1R antagonist AM251.

Centrally elicited hemodynamic effects of CB1R in conscious Sprague Dawley rats

In our recent studies, we sought to elucidate the mechanisms implicated in the central CB1R-evoked sympatoexcitation/pressor response [102,104,105]. In pursuit of this goal, we characterized the centrally mediated cardiovascular effects of central CB1R activation in conscious Sprague Dawley rats. We have confirmed the expression of CB1R (protein) in the RVLM by detecting the two bands at 64 and 53 kDa, which represent the N-glycosylated and non-glycosylated forms of CB1R, respectively (unpublished data) [106].

We reported that i.c. administration of WIN55,212-2 elicited dose-dependent pressor responses and increased NE plasma levels, denoting an increase in central sympathetic tone in conscious rats [102], which agrees with findings in experimental animals discussed above [39,101,103], and reflects similar responses observed in humans [47,48]. Similar pressor response was observed following microinjection of WIN55,212-2, for the first time, in the RVLM of conscious freely moving rats [104]. These studies were conducted in conscious rats to circumvent the negative impact of anesthesia that was shown to dramatically compromise cannabinoïd-evoked hemodynamic responses [36–38].

We demonstrated in our studies that the cardiovascular, biochemical, and molecular responses elicited by WIN55,212-2 were CB1R mediated. This is important because (i) WIN55,212-2, which is routinely used in cannabinoid research, can also bind to CB2R [107,108]; (ii) both CBR subtypes are expressed in the brain [89,109], including the brainstem [90]. The ability of the selective CB1R antagonist AM251 [39,101,103] to virtually abolish the pressor, biochemical and neurochemical responses elicited by i.c. WIN55,212-2 clearly implicates the CB1R in the observed responses. It is important to note, however, that the lack of change in blood pressure, as well as other biochemical
responses, following AM251 administration argues against the involvement of central CB1R signaling in tonic control of blood pressure in conscious rats [102,104,105].

Signaling mechanisms involved in CB1R-evoked pressor response in the RVLM

Role of ERK1/2-PI3K/Akt signaling pathway

Cannabinoids are highly potent activators of extracellular-signal regulated kinase 1/2 (ERK1/2), which was evident in stably transfected Chinese hamster ovary cells expressing human CB1R. This effect was (i) abrogated by SR141716A; (ii) sensitive to pertussis toxin; (iii) and independent of the cannabinoid-induced inhibition of cAMP production [110]. The pivotal role of PI3K/Akt and ERK1/2 as potential downstream molecular mediators of the central CB1R-mediated sympathoexcitation/pressor response as suggested by multiple lines of evidence was demonstrated recently [105]. Central administration of WIN55,212-2 (i.c.) significantly elevated pERK1/2 in the NTS and RVLM [105]. The involvement of any CB1R role in these responses was precluded because of the abrogation of the WIN55,212-2-mediated cardiovascular and neurochemical responses by MEK-ERK1/2 inhibition (PD98059) and attenuation of the concomitant activation of ERK1/2 pathway by pretreatment with the selective CB1R antagonist AM251 (i.c.). In view of the crucial role of brainstem pERK1/2 signaling in central control of blood pressure, previous studies from our laboratory [82,86] and others [111–113] suggest that brainstem ERK1/2 plays a bi-directional role in central regulation of blood pressure. For example, in both normometabolic and hypertensive rats, inhibition of RVLM ERK1/2 phosphorylation gradually lowered blood pressure [111], and its rapid activation plays pivotal role in the angiotensin II-mediated pressor response [113,114]. In contrast, we have previously shown that RVLM MEK-ERK1/2 signaling activation underlies the central 9α-adrenergic or imidazoline evoked acute hypotensive response [82,86].

Studies on the neuroprotective and/or anti-oncogenic effects of cannabinoids via PI3K/Akt signaling pathway have yielded controversial results. First, intraperitoneal injection of A2-THC activated PI3K/Akt pathway in mouse hippocampus, striatum, and cerebellum via a mechanism that was ERK1/2-independent [115]. Second, THC-mediated anti-cancer effect in human prostate cells involved PI3K/Akt and ERK1/2 signaling pathway activation [116]. On the other hand, it was demonstrated in multiple cancer cell lines that CB1R activation down regulates both PI3K/Akt and ERK1/2 signaling pathway [117,118]. Based on the molecular findings from our studies, we concluded that the effect of WIN55,212-2 on PI3K/Akt may contribute to the enhancement of ERK1/2 phosphorylation because in the presence of the PI3K/Akt inhibitor wortmannin, WIN55,212-2-induced ERK1/2 phosphorylation was exacerbated [105]. Additionally, PD98059, MEK-ERK1/2 inhibitor, alone or in the presence of WIN55,212-2 had no effect on brainstem pAkt phosphorylation levels.

Consistent with a diverse physiological role of PI3K/Akt-ERK1/2 pathway, we showed that a dose-related reduction in pAkt phosphorylation levels in the NTS and RVLM contributes to the i.c. WIN55,212-2-evoked pressor response [105]. In support of this conclusion are the findings that the inhibition of Akt phosphorylation in the NTS and RVLM preceded the peak WIN55,212-2-evoked pressor response (5 min). Our Western blot findings are consistent with reported findings that CB1R activation resulted in down-regulation of the PI3K/Akt signaling [105,117,118]. However, others have shown that CB1R activation up-regulated PI3K/Akt signaling in U373 MG human astrocytoma cells [119], hippocampal slices [120], and in vivo [115]. Nonetheless, further support for a causal role for the observed inhibition in Akt phosphorylation in the brainstem in the central CB1R-mediated pressor response are the findings that pharmacological inhibition of brainstem PI3K-Akt signaling (wortmannin) significantly enhanced the WIN55,212-2 evoked dose-related pressor response [105]. Interestingly, the latter study reported an increase in Akt phosphorylation elicited by WIN55,212-2 following CB1R blockade with AM251 in the NTS but not in the RVLM. This finding clearly highlights differences between neurochemical responses elicited by CB1R activation in the RVLM vs. NTS.

CB1R enhances RVLM nNOS-NO signaling pathway

The well-documented role of NOS-NO signaling in the RVLM regulation of autonomic function has led us to investigate whether nNOS-NO plays a significant role in the central CB1R-mediated pressor response [104,121–123]. We reported that intra-RVLM WIN55,212-2 microinjection elicited dose-dependent increases in real-time RVLM NO and blood pressure; NO was measured by in vivo electrochemistry and is possibly nNOS-generated because: (i) parallel to the WIN55,212-2 dose-dependent enhancement of NO release, we detected a significant increase in nNOS phosphorylation in the WIN55,212-2-treated RVLM compared to the contra-lateral side (control); (ii) i.e. WIN55,212-2 increased the number of nNOS-ir neurons expressing c-Fos, denoting an increase in the activity of nNOS expressing neurons; (iii) these neurochemical responses were abolished following selective CB1R blockade (AM251) or prior inhibition of nNOS phosphorylation (NPLA) [104]; (iv) only RVLM nNOS, but not eNOS or iNOS, derived NO is implicated in centrally evoked hypertension [123]. Because ERK1/2 dependent phosphorylation of RVLM nNOS is implicated in sympathoexcitation [124–126], the interesting possibility exists that CB1R-mediated nNOS activation might be downstream to MEK-ERK1/2 activation, which ultimately results in CB1R-mediated pressor response.

CB1R downregulates brainstem GABAergic transmission

It is highly likely that central CB1R-elicited sympathoexcitation is mediated via indirect modulation of presympathetic neurons in the brainstem whose activity is regulated by an array of tonic excitatory and inhibitory inputs [90,127]. Notably, CB1R regulates synaptic transmission of both inhibitory (GABA) and excitatory (glutamate) neurotransmitters [23,29,128,129]. Interestingly, stimulation of central GABA_A receptors (muscimol) caused the following: (i) abolished the CB1R-evoked pressor response and the elevation in plasma NE; (ii) attenuated the WIN55,212-2 evoked increase in the...
activity (c-Fos) of catecholamine (TH-ir) [102]. These findings are consistent with reported in vitro findings that demonstrated CB1R-evoked inhibition of GABAergic transmission in cultured rostral ventromedial medulla (RVM) neurons [31]. Yet, in the NTS, studies have demonstrated a controversial role for CB1R-mediated presynaptic modulation of excitatory (glutamate) and inhibitory (GABA) neurotransmitters. Anandamide increased baroreflex-mediated sympathoinhibition in the NTS, presumably, via presynaptic inhibition of GABA release because the response was reversed in presence of the GABA_A receptor antagonist [52].

Conclusions

As summarized in Fig. 1, the present review highlights the molecular mechanisms implicated in the predominant sympathoexcitatory effect of brainstem CB1R activation in conscious rats. CB1R stimulation enhanced neuronal activity of presynaptic neurons in the RVLM (c-Fos/TH-ir ratio). Furthermore, PI3K/Akt-ERK1/2 signaling in the brainstem seems to differentially contribute, at least in part, to the sympathoexcitatory responses elicited by the central CB1R activation in conscious rats. The discussed studies demonstrated that CB1R activation in the RVLM elicits down-regulation of PI3K/Akt pathway along with the pressor response, which was supported by the exacerbation of WIN55,212-2 evoked hemodynamic responses when PI3K/Akt was inhibited by wortmannin. By contrast, the CB1R-evoked sympathoexcitation was associated with enhanced ERK1/2 activity in the brainstem. Further, suppressing ERK1/2 signaling abolished the central CB1R-evoked pressor response. Finally, CB1R activation in the RVLM enhanced neuronal nitrooxidergic activity (nNOS-NO) essential for the central regulation of cardiovascular function. These latter neuronal responses may be linked to the modulation of brainstem GABAergic neurotransmission and subsequently to the central CB1R-evoked sympathoexcitatory and pressor response. It is imperative to note that this overview highlights important signaling networks implicated in the modulation of blood pressure caused by central CB1R activation in normotensive rats. The neurochemical and molecular responses discussed above might be different under pathophysiological conditions and might, therefore, lead to different cardiovascular outcomes. Therefore, future studies on the role of central CB1R signaling in animal models of human diseases are warranted.

Conflict of interest

The authors have declared no conflict of interest.

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References

[1] Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature 1993;365(6441): 61–5.
[2] Felder CC, Joyce KE, Briley EM, Mansouri J, Mackie K, Blond O, et al. Comparison of the pharmacology and signal transduction of the human cannabinoid CB1 and CB2 receptors. Mol Pharmacol 1995;48(3):443–50.
[3] Devane W, Hanus L, Breuer A, Pertwee R, Stevenson L, Griffin G, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 1992;258(5090):1946–9.
[4] Sugiura T, Kodaka T, Nakane S, Miyashita T, Kondo S, Suhara Y, et al. Evidence that the cannabinoid CB1 receptor is a 2-arachidonoylglycerol receptor. J Biol Chem 1999;274(5):61–5.
[5] Porte AA, Sauer J-M, Knierman MD, Becker GW, Berna MJ, Bao J, et al. Characterization of a novel endocannabinoid, virodhamine, with antagonist activity at the CB1 receptor. J Pharmacol Exp Ther 2002;301(3):1020–4.
[6] Rinaldi-Carmona M, Barth F, Millan J, Derocq J-M, Casellas P, Congy C, et al. SR 144528, the first potent and selective antagonist of the CB2 cannabinoid receptor. J Pharmacol Exp Ther 1998;284(2):644–50.
[7] Pertwee RG, Gibson TM, Stevenson LA, Ross RA, Banner WK, Saha B, et al. O-1057, a potent water-soluble...
cannabinoid receptor agonist with antinoceptive properties. Br J Pharmacol 2000;129(8):1577–84.

[8] Dodd GT, Mancini G, Lutz B, Luckman SM. The peptide hemorphisin acts through CB1 cannabinoid receptors to reduce food intake in rats and mice. J Neurosci 2010;30(21):7369–76.

[9] Heimann AS, Gomes I, Dale CS, Pagano RL, Gupta A, de Souza LL, et al. Hemorphisin is an inverse agonist of CB1 cannabinoid receptors. Proc Nat Acad Sci 2007;104(51):20588–93.

[10] Laukner JE, Jensen JB, Chen HY, Lu HC, Hille B, Mackie K. GPA55 is a cannabinoid receptor that increases intracellular calcium and inhibits M current. Proc Nat Acad Sci USA 2008;105(7):2699–704.

[11] Jarai Z, Wagner JA, Varga K, Lake KD, Compton DR, Martin BR, et al. Cannabinoid-induced mesenteric vasodilation through an endothelial site distinct from CB1 or CB2 receptors. Proc Nat Acad Sci USA 1999;96(24):14136–41.

[12] Kapur A, Zhao PW, Sharir H, Bai YS, Caron MG, Barak LS, et al. Atypical responsiveness of the orphan receptor GPR55 to cannabinoids. J Biol Chem 2009;284(43):29817–27.

[13] Ryberg E, Larsson N, Sjogren S, Hjorth S, Hermansson NO, Leonova J, et al. The orphan receptor GPR55 is a novel cannabinoid receptor. Br J Pharmacol 2007;152(7):1092–101.

[14] Waldeck-Weiermair M, Zoratti C, Osibow K, Balenga N, Goesnitzer E, Waldhoer M, et al. Integrin clustering enables anandamide-induced Ca(2+) signaling in endothelial cells via GPR55 by protection against CB1-receptor-triggered repression. J Cell Physiol 2008;121(10):1704–17.

[15] Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 1990;346(6284):561–4.

[16] Gerard CM, Mollereau C, Vassart G, Parmentier M. Molecular cloning of a human cannabinoid receptor which is also expressed in testis. Biochem J 1991;279(Pt 1):129–34.

[17] Howlett AC. The CB1 cannabinoid receptor in the brain. Neurobiol Dis 1998;5(6):405–16.

[18] Bidaut-Russell M, Devane WA, Howlett AC. Cannabinoid receptors and modulation of cyclic AMP accumulation in the rat brain. J Neurochem 1990;55(1):21–6.

[19] Howlett AC, Qualy JM, Khachatrian LL. Involvement of Gi in the inhibition of adenylate cyclase by cannabinoid drugs. Mol Pharmacol 1986;29(3):307–13.

[20] Childers SR, Fleming L, Konkoy C, Marckel D, Pacheco M, Sexton T, et al. Opioid and cannabinoid receptor inhibition of adenyl cyclase in brain. Ann NY Acad Sci 1992;654(1):33–51.

[21] Felder CC, Joyce KE, Briley EM, Glass M, Mackie KP, Fahey KJ, et al. LY331285, a novel cannabinoid CB1 receptor antagonist, unmasks coupling of the CB1 receptor to stimulation of AMP accumulation. J Pharmacol Exp Ther 1998;284(1):291–7.

[22] Howlett AC, Mukhopadhyay S. Cellular signal transduction by anandamide and 2-arachidonoylglycerol. Chem Phys Lipids 2000;108(1–2):53–70.

[23] Piomelli D. The molecular logic of endocannabinoid signalling. Nat Rev Neurosci 2003;4(11):873–84.

[24] Laukner JE, Hille B, Mackie K. The cannabinoid agonist WIN55,212-2 increases intracellular calcium via CB1 receptor coupling to Gq/11 G proteins. Proc Nat Acad Sci USA 2003;102(52):19144–9.

[25] Kearn CS, Blake-Palmer K, Daniel E, Mackie K, Glass M. Concurrent stimulation of cannabinoid CB1 and dopamine D2 receptors enhances heterodimer formation: a mechanism for receptor cross-talk? Mol Pharmacol 2005;67(5):1697–704.

[26] Glass M, Felder CC. Concurrent stimulation of cannabinoid CB1 and dopamine D2 receptors augments cAMP accumulation in striatal neurons: evidence for a Gs linkage to the CB1 receptor. J Neurosci 1997;17(14):5327–33.

[27] McIntosh BT, Hudson B, Yegorova S, Jollimore CB, Kelly MEM. Agonist-dependent cannabinoid receptor signalling in human trabecular meshwork cells. Br J Pharmacol 2007;152(7):1111–20.

[28] Ellis J, Pediani JD, Canals M, Milasta S, Milligan G. Orexin-1 receptor-cannabinoid CB1 receptor heterodimerization results in both ligand-dependent and -independent coordinated alterations of receptor localization and function. J Biol Chem 2006;281(50):38812–24.

[29] Freund TF, Katona I, Piomelli D. Role of endogenous cannabinoids in synaptic signaling. Physiol Rev 2003;83(3):1017–66.

[30] Ohno-Sosaku T, Maejima T, Kano M. Endogenous cannabinoids mediate retrograde signals from depolarized postsynaptic neurons to presynaptic terminals. Neuron 2001;29(3):729–38.

[31] Vaughan CW, McGregor IS, Christie MJ. Cannabinoid receptor activation inhibits GABAergic neurotransmission in rostral ventromedial medulla neurons in vitro. Br J Pharmacol 1999;127(4):935–40.

[32] Kreitzer AC, Regehr WG. Retrograde inhibition of presynaptic calcium influx by endogenous cannabinoids at excitatory synapses onto purkinje cells. Neuron 2001;29(3):717–27.

[33] Mendizabal VE, Adler-Graschinsky E. Cannabinoids as therapeutic agents in cardiovascular disease: a tale of passions and illusions. Br J Pharmacol 2007;151(4):427–40.

[34] Randall MD, Kendall DA, O’Sullivan S. The complexities of the cardiovascular actions of cannabinoids. Br J Pharmacol 2004;142(1):20–6.

[35] Randall MD, Harris D, Kendall DA, Ralevic V. Cardiovascular effects of cannabinoids. Pharmacol Ther 2002;95(2):191–202.

[36] Stein EA, Fuller SA, Edgemond WS, Campbell WB. Physiological and behavioural effects of the endogenous cannabinoid, arachidonylethanolamide (anandamide), in the rat. Br J Pharmacol 1996;119(1):107–14.

[37] Gardiner SM, March JE, Kemp PA, Bennett T. Regional haemodynamic responses to the cannabinoid agonist, WIN 55212-2, in conscious, normotensive rats, and in hypertensive, transgenic rats. Br J Pharmacol 2001;133(3):445–53.

[38] Lake KD, Martin BR, Kunos G, Varga K. Cardiovascular effects of anandamide in anesthetized and conscious normotensive and hypertensive rats. Hypertension 1997;29(5):1204–10.

[39] Niederhoffer N, Szabo B. Effect of the cannabinoid receptor agonist WIN55212-2 on sympathetic cardiovascular regulation. Br J Pharmacol 1999;126(2):457–66.

[40] Varga K, Lake KD, Huangfu D, Guyenet PG, Kunos G. Mechanism of the hypotensive action of anandamide in anesthetized rats. Hypertension 1996;28(4):682–6.

[41] Lake KD, Compton DR, Varga K, Martin BR, Kunos G. Cannabinoid-induced hypotension and bradycardia in rats mediated by CB1-like cannabinoid receptors. J Pharmacol Exp Ther 1997;281(3):1030–7.

[42] Varga K, Lake K, Martin BR, Kunos G. Novel antagonist implicates the CB1 cannabinoid receptor in the hypotensive action of anandamide. Eur J Pharmacol 1995;278(3):279–83.

[43] Siqueira SW, Lapa AJ, Ribeiro do Valle J. The triple effect of delta 9-tetrahydrocannabinol on the rat blood pressure. Eur J Pharmacol 1979;58(4):351–7.

[44] Kwolek G, Zakrajsek A, Schlicker E, Goethert M, Godlewski G, Malinowska B. Central and peripheral components of the pressor effect of anandamide in urethane-anaesthetized rats.[see comment]. Br J Pharmacol 2005;145(5):567–75.

[45] Malinowska B, Zakrajsek A, Kurz C, Göthert M, Kwolek G, Wielgat P, et al. Involvement of central β2 adrenergic, NMDA
and thromboxane A2 receptors in the pressor effect of
anandamide in rats. Naunyn Schmiedebergs Arch Pharacol
2010;381(4):349–60.

[46] Benowitz NL, Rosenberg J, Rogers W, Bachman J, Jones RT.
Cardiovascular effects of intravenous delta-9-tetrahydro-
cannabinol: autonomic nervous mechanisms. Clin Pharmacol
Ther 1979;25(4):440–6.

[47] Foltin RW, Fischman MW, Pedroso JJ, Pearlson GD. Marijuana and
cocaine interactions in humans: cardiovascular consequences.
Pharmacol Biochem Behav 1987;28(4):459–64.

[48] Sidney S. Cardiovascular consequences of marijuana use. J
Clin Pharmacol 2002;42(9010):S64–70.

[49] Dean C. Cannabinoid and GABA modulation of sympathetic
nerve activity and blood pressure in the dorsal periaqueductal
gray of the rat. Am J Physiol Regul Integr Comp Physiol
2011;301(6):R1765–72.

[50] Seagard JL, Hopp FA, Hillard CJ, Dean C. Effects of
endocannabinoids on discharge of baroreceptive NTS
neurons. Neurosci Lett 2005;381(3):334–9.

[51] Rademacher DJ, Patel S, Hopp FA, Dean C, Hillard CJ,
Seagard JL. Retrograde injection of a cannabinoid receptor
antagonist into the NTS increases baroreflex duration in
dogs. Am J Physiol – Heart Circulat Physiol 2003;284(5):
H1570–6.

[52] Seagard JL, Dean C, Patel S, Rademacher DJ, Hopp FA,
Schmeling WT, et al. Anandamide content and interaction of
endocannabinoid/GABA modulatory effects in the NTS on
baroreflex-evoked sympathoinhibition. Am J Physiol – Heart
Circulat Physiol 2004;286(3):H992–1000.

[53] Aicher SA, Randich A. Antinociception and cardiovascular
responses produced by electrical stimulation in the nucleus
tractus solitarius, nucleus reticularis ventralis, and the caudal
medulla. Pain 1990;42(1):103–19.

[54] Miura M, Reis DJ. The role of the solitary and paramedian
reticular nuclei in mediating cardiovascular reflex responses from
carotid baro- and chemoreceptors. J Physiol 1972;223(2):
525–48.

[55] Nomura S, Mizuno N. Central distribution of afferent and
efferent components of the glossopharyngeal nerve: an HRP
study in the cat. Brain Res 1982;256(1):1–13.

[56] Seiders EP, Stuesse SL. A horseradish peroxidase investigation of
carotid sinus nerve components in the rat. Neurosci Lett
1984;46(1):13–8.

[57] Aicher SA, Sarayav RH, Cravo SL, Reis DJ, et al. Monosynaptic
projections from the nucleus tractus solitarii to C1 adrenergic neurons in the rostral
ventrolateral medulla: comparison with input from the caudal ventrolateral medulla. J Comp Neurol 1996;373(1):62–75.

[58] Aicher SA, Kurucz OS, Reis DJ, Milner TA. Nucleus tractus
solitarius efferent terminals synapse on neurons in the caudal
ventrolateral medulla that project to the rostral ventrolateral
medulla. Brain Res 1995;693(1–2):51–63.

[59] Dampney RA, Czaczsuk I, Dembowsky K, Goodchild AK,
Seller H. Afferent connections and spinal projections of the pressor region in the rostral ventrolateral medulla of the cat. J
Auton Nerv Syst 1987;20(1):73–86.

[60] Ross CA, Ruggiero DA, Reis DJ. Projections from the nucleus
tractus solitarii to the rostral ventrolateral medulla. J Comp Neurol 1985;242(4):511–34.

[61] Van Sickle MD, Oland LD, Ho W, Hillard CJ, Mackie K,
Davison JS, et al. Cannabinoids inhibit emesis through CB1
receptors in the brainstem of the ferret. Gastroenterology
2001;121(4):767–74 [see comment].

[62] Chen C-Y, Bonham AC, Dean C, Hopp FA, Hillard CJ,
Seagard JL. Retrograde release of endocannabinoids inhibits
presynaptic GABA release to second-order baroreceptive
neurons in NTS. Auton Neurosci 2010;158(1–2):44–50.

[63] Nassar N, Abdel-Rahman AA. Central adenosine signaling plays a key role in centrally mediated hypotension in conscious aortic barodenervated rats. J Pharmacol Exp Ther 2006;318(1):255–61.

[64] Dampney RA, Polson JW, Potts PD, Hirooka Y, Horiiuchi J.
Functional organization of brain pathways subserving the
baroreceptor reflex: studies in conscious animals using immediate early gene expression. Cell Mol Neurobiol 2003;23(4–5):597–616.

[65] Strack AM, Sawyer WB, Hughes JH, Platt KB, Loewy AD. A
general pattern of CNS innervation of the sympathetic outflow demonstrated by transneuronal pseudorabies viral infections. Brain Res 1989;491(1):156–62.

[66] Guyenet PG, Haselton JR, Sun MK. Sympathoexcitatory
neurons of the rostroventrolateral medulla and the origin of the sympathetic vasomotor tone. Prog Brain Res 1989;81:105–16.

[67] Farlow DM, Goodchild AK, Dampney RA. Evidence that
vasomotor neurons in the rostral ventrolateral medulla project to the spinal sympathetic outflow via the dorsomedial pressor area. Brain Res 1984;298(2):313–20.

[68] Andrezik JA, Chan-Palay V, Palay SL. The nucleus
paragigantocellularis lateralis in the rat. Anat Embryol
1981;161(4):355–71.

[69] Villanueva L, de Pommery J, Menétrey D, Le Bars D. Spinal
afferent projections to subnucleus reticularis dorsalis in the rat. Neurosci Lett 1991;134(1):98–102.

[70] Watanae S, Kitamura T, Watanae L, Sato H, Yamada J. Projections from the nucleus reticularis magnocellularis to the
rat cervical cord using electrical stimulation and iontophoretic injection methods. Anatom Sci Int 2003;78(1):42–52.

[71] Ruggiero DA, Cravo SL, Arango V, Reis DJ. Central control
of the circulation by the rostral ventrolateral reticular nucleus: anatomical substrates. Prog Brain Res 1989;81:49–79.

[72] Ross CA, Ruggiero DA, Joh TH, Park DH, Reis DJ. Rostral
ventrolateral medulla: selective projections to the thoracic
autonomic cell column from the region containing C1
adrenergic neurons. J Comp Neurol 1984;228(2):168–85.

[73] Jeske I, McKenna KE. Quantitative analysis of bulbovascular
projections from the rostral ventrolateral medulla: contribution of
C1-adrenergic and nonadrenergic neurons. J Comp Neurol 1992;324(1):1–13.

[74] Kanjhan R, Lipski J, Kruszewska B, Rong W. A comparative
study of pre-sympathetic and Bötzinger neurons in the rostral
ventrolateral medulla (RVLM) of the rat. Brain Res 1995;699(1):19–32.

[75] Schrehofer AM, Guyenet PG. Identification of C1
presympathetic neurons in rat rostral ventrolateral medulla by
juxtcacellular labeling in vivo. J Comp Neurol 1997;387(4):524–36.

[76] Guyenet PG. The sympathetic control of blood pressure. Nat
Rev Neurosci 2006;7(5):335–46.

[77] Guyenet PG, Koshiya N, Huangfu D, Baraban SC, Stornetta
RBG, Saper CB, editors. Progress in brain research. Elsevier; 1997.
p. 127–44
Karlsson GA, Preuss CV, Chaitoff KA, Maher TJ, Ally A. Vasodepressor and pressor responses to drugs topically applied to the ventral surface of the brain stem. J Physiol – Regul Integrat Comp Physiol 2000;279(4):R1392–402.

Zhang J, Abdel-Rahman AA. The hypotensive action of rilmenidine is dependent on functional N-methyl-D-aspartate receptor in the rostral ventrolateral medulla of conscious spontaneously hypertensive rats. J Pharmacol Exp Ther 2002;303(1):204–10.

Zhang J, Abdel-Rahman AA. Mitogen-activated protein kinase phosphorylation in the rostral ventrolateral medulla plays a key role in imidazole (ii)-receptor-mediated hypotension. J Pharmacol Exp Ther 2005;314(3):945–52.

El-Mas MM, Abdel-Rahman AA. Differential modulation by estrogen of alpha2-adrenergic and II-imidazole receptor-mediated hypotension in female rats. J Appl Physiol 2004;97(4):1237–44.

Li G, Wang X, Abdel-Rahman AA. Neuronal norepinephrine responses of the rostral ventrolateral medulla and nucleus tractus solitarii neurons distinguish the II- from the alpha2-receptor-mediated hypotension in conscious SHR. J Cardiovasc Pharmacol 2005;46(1):52–62.

Herkenham M, Lynn AB, Johnson MR, Melvin LS, de Costa DR. Autoradiographic study. J Neurosci 1991;11(2):563–83.

Padley JR, Li Q, Pilowsky PM, Goodchild AK. Cannabinoid receptor activation in the rostral ventrolateral medulla oblongata evokes cardiorespiratory effects in anaesthetised rats. Br J Pharmacol 2003;140(2):384–94.

Van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, Mackie K, et al. Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science 2005;310(5746):329–32.

Drake CT, Aicher SA, Montalmant FL, Milner TA. Redistribution of mu-opioid receptors in C1 adrenergic neurons following chronic administration of morphine. Exp Neurol 2005;196(2):365–72.

Aicher SA, Kraus JA, Sharma S, Patel A, Milner TA. Selective distribution of mu-opioid receptors in C1 adrenergic neurons and their afferents. J Comp Neurol 2001;433(1):23–33.

Guertzenstein PG, Silver A. Distribution of mu-opioid receptors in C1 adrenergic neurons from discrete regions of the ventral surface of the medulla by glycinene and lesions. J Physiol 1974;242(2):489–503.

Feldberg W, Guertzenstein PG. Vasodepressor effects obtained by drugs acting on the ventral surface of the brain stem. J Physiol 1976;258(2):337–55.

Guertzenstein PG. Vasodepressor and pressor responses to drugs topically applied to the ventral surface of the brain stem. J Physiol 1972;234(2):84P–59.

McAllen RM, Dampney RA. The selectivity of descending vasomotor control by subfretocanial neurons. Prog Brain Res 1989;81:233–42.

Carlsson GA, Preuss CV, Chaitoff KA, Maher TJ, Ally A. Medullary monoamines and NMDA-receptor regulation of cardiovascular responses during peripheral nociceptive stimuli. Neurosci Res 2006;55(3):316–26.

Javanmardi K, Parviz M, Sadr Ss, Keshavarz M, Minaii B, Dehpour AR. Involvement of N-methyl-D-aspartate receptors and nitric oxide in the rostra ventromedial medulla in modulating morphine pain-inhibitory signals from the periaqueductal grey matter in rats. Clin Exp Pharmacol Physiol 2005;32(4):785–9.

Nattie EE, Li AH. Fluorescence location of RVLM kainate microinjections that alter the control of breathing. J Appl Physiol 1990;68(3):1157–66.

Niederhoffer N, Szabo B. Cannabinoids cause central sympathoexciitation and bradycardia in rabbits. J Pharmacol Exp Ther 2000;294(2):707–13.

Ibrahim BM, Abdel-Rahman AA. Role of brainstem GABAergic signaling in central cannabinoid receptor evoked sympathoexcitation and pressor responses in conscious rats. Brain Res 2011;1414:1–9.

Pfizer T, Niederhoffer N, Szabo B. Central effects of the cannabinoid receptor agonist WIN55212-2 on respiratory and cardiovascular regulation in anaesthetised rats. Br J Pharmacol 2004;142(6):943–52.

Ibrahim BM, Abdel-Rahman AA. Enhancement of rostral ventrolateral medulla neuronal nitric-oxide synthase-nitric-oxide signaling mediates the central cannabinoid receptor 1-evoked pressor response in conscious rats. J Pharmacol Exp Ther 2012;341(3):579–86.

Ibrahim BM, Abdel-Rahman AA. Differential modulation of brainstem PI3K/Akt and ERK1/2 signaling underlies WIN55,212-2 centrally-mediated pressor response in conscious rats. J Pharmacol Exp Ther 2012;340(1):11–8.

Song C, Howlett A. Rat brain cannabinoid receptors are N-linked glycosylated proteins. Life Sci 1995;56(23-24):1983–9.

Griffin G, Atkinson PJ, Showalter VM, Martin BR, Aboud ME. Evaluation of cannabinoid receptor agonists and antagonists using the guanosine-5′-O-(3-[35S]thio)-triphosphate binding assay in rat cerebellar membranes. J Pharmacol Exp Ther 1998;285(2):553–60.

Showalter VM, Compton DR, Martin BR, Aboud ME. Evaluation of binding in a transfected cell line expressing a peripheral cannabinoid receptor (CB2): identification of cannabinoid receptor subtype selective ligands. J Pharmacol Exp Ther 1989;278(3):989–99.

Viscomi MT, Oddi S, Latini L, Pasquariello N, Florenzano F, Bernardi G, et al. Selective CB2 receptor agonist promotes central neurons from remote axotomy-induced apoptosis through the PI3K/Akt Pathway. J Neurosci 2009;29(14):4564–70.

Bouaboula M, Point-Chazel C, Bourrie B, Canat X, Calandra B, Rinaldi-Carmona M, et al. Activation of mitogen-activated protein kinases by stimulation of the central cannabinoid receptor CB1. Biochem J 1995;312(Pt 2):637–41.

Seyedabadi M, Goodchild AK, Pilowsky PM. Differential role of kinases in brain stem of hypertensive and normotensive rats. Hypertension 2001;38(5):1087–92.

Lin YZ, Matsumura K, Tsuchihashi T, Fukuhara M, Fujii K, Iida M. Role of ERK and Rho kinase pathways in central sympatoexcitation and bradycardia in rabbits. J Pharmacol Exp Ther 2002;303(1):204–10.

Shan SH, Wang L-L, Tseng H-L, Chan JY. Uregulation of AT1 receptor gene on activation of protein kinase C(beta)/nicotinamide adenine dinucleotide diphosphate oxidase/ERK1/2/c-fos signaling cascade mediates long-term pressor effect of angiotensin II in rostral ventrolateral medulla. J Hypertens 2007;25(9):1845–61.

Shan SHH, Hsu K-S, Huang C-C, Wang L-L, Ou C-C, Chan JYH. NADPH oxidase-derived superoxide anion mediates angiotensin II-induced pressor effect via activation of p38.
Central CB₁R-mediated pressor response

[115] Ozaita A, Puighermanal E, Maldonado R. Regulation of PI3K/Akt/GSK-3 pathway by cannabinoids in the brain. J Neurochem 2007;102(4):1105–14.

[116] Sanchez MG, Ruiz-Llorente L, Sanchez AM, Diaz-Laviada I. Activation of phosphoinositide 3-kinase/PKB pathway by CB₁(1) and CB₁(2) cannabinoid receptors expressed in prostate PC₃ cells. Involvement in Raf-1 stimulation and NGF induction. Cell Signal 2003;15(9):851–9.

[117] Ellert-Miklaszewska A, Kaminska B, Konarska L. Cannabinoids down-regulate PI3K/Akt and Erk signalling pathways and activate proapoptotic function of Bad protein. Cell Signal 2005;17(1):25–37.

[118] Greenhough A, Patsos HA, Williams AC, Paraskeva C. The cannabinoid delta(9)-tetrahydrocannabinol inhibits RAS-MAPK and PI3K-AKT survival signalling and induces BAD-mediated apoptosis in colorectal cancer cells. Int J Cancer 2007;121(10):2172–80.

[119] Galve-Roperh I, Rueda D, Gomez del Pulgar T, Velasco G, Guzman M. Mechanism of extracellular signal-regulated kinase activation by the CB₁ cannabinoid receptor. Mol Pharmacol 2002;62(6):1385–92.

[120] Derkinderen P, Valjent E, Toutant M, Corvol JC, Enslen H, Ledent C, et al. Regulation of extracellular signal-regulated kinase by cannabinoids in hippocampus. J Neurosci 2003;23(6):2371–82.

[121] Martins-Pinge MC, Araujo GC, Lopes OU. Nitric oxide-dependent guanylyl cyclase participates in the glutamatergic neurotransmission within the rostral ventrolateral medulla of awake rats. Hypertension 1999;34(4):748–51.

[122] Mayorov DN. Nitric oxide synthase inhibition in rostral ventrolateral medulla attenuates pressor response to psychological stress in rabbits. Neurosci Lett 2007;424(2):89–93.

[123] Martins-Pinge MC, Garcia MR, Zoceal DB, Crestani CC, Pinge-Filho P. Differential influence of iNOS and nNOS inhibitors on rostral ventrolateral medullary mediated cardiovascular control in conscious rats. Auton Neurosci-Basic Clin 2007;131(1–2):65–9.

[124] Chan JYH, Chan SHH, Chang AYW. Differential contributions of NOS isoforms in the rostral ventrolateral medulla to cardiovascular responses associated with mevinphos intoxication in the rat. Neuropharmacology 2004;46(8):1184–94.

[125] Chan SH, Sun EY, Chang AY. Extracellular signal-regulated kinase 1/2 plays a pro-life role in experimental brain stem death via MAPK signal-interacting kinase at rostral ventrolateral medulla. J Biomed Sci 2010;17:17.

[126] Chan JYH, Chan SHH, Li FCH, Tsai CY, Cheng HL, Chang AYW. Phasic cardiovascular responses to mevinphos are mediated through differential activation of cGMP/PKG cascade and peroxynitrite via nitric oxide generated in the rat rostral ventrolateral medulla by NOS I and II isoforms. Neuropharmacology 2005;48(1):161–72.

[127] Pilowsky PM, Goodchild AK. Baroreceptor reflex pathways and neurotransmitters: 10 years on. J Hypertens 2002;20(9):1675–88.

[128] Drew GM, Mitchell VA, Vaughan CW. Glutamate spillover modulates GABAergic synaptic transmission in the rat midbrain periaqueductal grey via metabotropic glutamate receptors and endocannabinoid signaling. J Neurosci 2008;28(4):808–15.

[129] Jelsing J, Galzin A-M, Guillot E, Pruniaux M-P, Larsen PJ, Vrang N. Localization and phenotypic characterization of brainstem neurons activated by rimonabant and WIN55,212-2. Brain Res Bull 2009;78(4–5):202–10.

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