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Beta-adrenergic receptor activation increases GABA uptake in adolescent mice frontal cortex: Modulation by cannabinoid receptor agonist WIN55, 212-2

Robertta Silva Martins[a], Isis Grigorio de Freitas[b], Matheus Figueiredo Sathler[a,g], Vladimir Pedro Peralva Borges Martins[a], Clarissa de Sampaio Schitine[c], Luzia da Silva Sampaio[d], Hércules Rezende Freitas[d], Alex Christian Manhães[e], Maurício dos Santos Pereira[f], Ricardo Augusto de Melo Reis[d], Regina Célia Cussa Kubrusly[a,*]

[a] Laboratório de Neurofarmacologia, Departamento de Fisiologia e Farmacologia, Pós-Graduação em Neurociências, Universidade Federal Fluminense, Niterói, Brazil
[b] Laboratório de Neurogênese, Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Brazil
[c] Laboratório de Neuroanatomia Celular, Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Brazil
[d] Laboratório de Neuroquímica, Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Brazil
[e] Laboratório de Neurofisiologia, Instituto de Biologia Roberto Alcantara Gomes, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil
[f] Laboratório de Neurofisiologia Molecular, Departamento de Morfologia, Fisiologia e Patologia Básica, Faculdade de Odontologia de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, Brazil
[g] Department of Biomedical Sciences, Colorado State University, Fort Collins, CO, 80523, United States

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ABSTRACT

GABA transporters regulate synaptic GABA levels and dysfunctions in this system might result in psychiatric disorders. The endocannabinoid system (ECS) is the main circuit breaker in the nervous system and may alter noradrenaline (NA) communication, which in turn modulates the release of GABA. However, a close relationship between these systems has not been recognized. We asked whether NA and ECS might control extracellular GABA levels in slices of frontal cortex (FC) of adolescent Swiss mice with 40 days after birth (PN40). Here we show that NA and isoproterenol (ISO), a beta-adrenergic agonist, increased [^{3}H]-GABA uptake in mice FC, while alpha$_1$-adrenergic agonist phenylephrine had no effect. As GAT-1 is expressed and fully functional at the FC, addition of NO-711, a GAT-1 inhibitor, dose dependently blocked [^{3}H]-GABA uptake. The increase of [^{3}H]-GABA uptake induced by ISO was also blocked by NO-711. [^{3}H]-GABA release induced by 80 mM KCl was reduced by NO-711, but not by removal of Ca^{2+}. ISO also increased cyclic AMP (cAMP) levels and addition of WIN 55,212-2, a mixed CB_1/CB_2 receptor agonist, inhibited the effect of ISO in GABA uptake increase, GAT-1 expression and cAMP levels compared to control. Our data show that GABA transport increased by NA and ISO is negatively regulated by cannabinoid receptor agonist WIN55,212-2.

1. Introduction

Adolescence is a critical developmental period during which cortical maturation is under neural, hormonal and behavioral influence (Doremus-Fitzwater et al., 2010). While glutamate is the major transmitter in circuitries, GABAergic synapses remain under construction, leading to immature and impulsive behavior that is so common to adolescent life (Arain et al., 2013). The refinement of GABAergic system, therefore, is gaining significant attention as a potential moderator of human developmental changes in impulse control, self-regulation and decision-making (Silveri, 2014). In the mature central nervous system (CNS), GABA is the main inhibitory neurotransmitter with major roles in neuronal excitability, information processing and neuronal plasticity (Ko et al., 2015; Melone et al., 2015). Dysfunctions

Abbreviation list: GABA, γ-Aminobutyric acid; ECS, endocannabinoid system; NA, noradrenaline; FC, frontal cortex; PN40, 40 days after birth or adolescence; cAMP, cyclic adenosine 3″,5″-monophosphate; CNS, central nervous system; GATs, GABA transporters; IBMX, (3-isobutyl-1-methylxanthine); PKA, protein kinase A; PKC, protein kinase C; GPCR, G protein-coupled receptor family; AEA, anandamide; 2-AG, 2-arachidonoylglycerol; CB_1, CB_1 receptor; CB_2, CB_2 receptor; Beta-ADR, beta-adrenergic receptor; Alpha$_1$-ADR, alpha$_1$ adrenergic receptor; WIN, WIN 55,212-2; ISO, Isoproterenol; PHE, Phenylephrine; DOB, Dobutamine; SAL, Salbutamol

* Corresponding author. Laboratório de Neurofarmacologia, Rua Hernani Pires de Melo 101, 215, São Domingos, Niterói, RJ, CEP. 24210-130, Brazil.
E-mail address: reginakubrusly1@gmail.com.br (R.C.C. Kubrusly).

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