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Research paper

Are presynaptic GABA-Cρ2 receptors involved in anti-nociception?

R. Tadavarty[a], J. Hwang[a], P.S. Rajput[b], P.J. Soja[b], U. Kumar[b], B.R. Sastry[a,*]

[a] Neuroscience Research Laboratory, Department of Anesthesiology, Pharmacology and Therapeutics, Faculty of Medicine, The University of British Columbia, Vancouver, BC, Canada
[b] Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, BC, Canada

HIGHLIGHTS

- GABA-C receptors are anti-nociceptive.
- The ρ2 type are expressed presynaptically in lumbar dorsal horn of the spinal cord.
- Analgesic effects could be via control of nociceptive input in substantia gelatinosa.

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ABSTRACT

We investigated the anti-nociceptive effects of GABA-C receptors in the central nervous system. Intracisternal injection of CACA, a GABA-C receptor agonist or isoguvacine, a GABA-A receptor agonist, significantly increased the tail-withdrawal latency. TPMPA, a GABA-C receptor antagonist blocked the effects of CACA but not isoguvacine indicating that GABA-C receptors are involved in regulating pain. Further, double-labelled immunofluorescence studies revealed that GABA-Cρ2 receptors are expressed presynaptically in the spinal dorsal horn, especially, substantia gelatinosa, a region that has been previously implicated in analgesia by regulating nociceptive inflow. These data provide a provenance for future work looking at presynaptic spinal GABA-C receptors in the control of nociception.

1. Introduction

γ-Amino butyric acid (GABA), in the mammalian central nervous system (CNS), exerts fast synaptic inhibition via actions on two distinct receptor subtypes: GABA-A and GABA-C rho (ρ) receptors. They are both Cl^- permeable ionotropic receptors, but differ in biophysical, pharmacological and physiological properties [11]. The GABA-A receptor is a hetero-oligomeric and pentameric assembly of α1–α6, β1–β3, γ1–γ3, δ, ϵ, θ and π, subunits [22], whereas, GABA-C receptors are mainly a homo-, hetero- or hetero-oligo -meric assembly of ρ1-ρ3, subunits [14]. GABA-A and GABA-C receptors can also co-assemble as a functional receptor [24]. GABA-C receptors, are activated by *cis*- and *trans*- enantiomers, of GABA analogue 4-aminocrotonic acid, CACA and TACA [16], blocked competitively by (1,2,5,6-tetrahydropyridine-4-yl) methylphosphinic acid, TPMPA [28], and modulated by divalent cations [3,7,17]. They are insensitive to GABA-A receptor antagonist bicuculline, allosteric modulators, such as, benzodiazepines and barbiturates [39], and only weakly modulated by neuroactive steroids [23].

Although, GABA-C receptors were originally described in the spinal cord [16], clues to their physiological function arise mainly from studies in the visual system [5,26]. In mammals, GABA-C receptors are found abundantly in cone photoreceptors and bipolar cell axon terminals, where they participate in GABAergic feed-back inhibition from horizontal cells and amacrine cells, respectively [21,25]. Perhaps due to a region-specific differential expression of these receptors, GABA elicits mixed GABA-A and GABA-C receptor currents in bipolar cells [10,38]. The slower kinetics of GABA-C receptors when coupled to fast, transient actions of GABA-A receptors, helps maintain the fidelity in visual information processing, by allowing precise controls over spatio-temporal filtering of synaptic input into the retinal ganglionic cells [6,38]. In the CA1 region of the hippocampus, they have been shown to block the paired-pulse depression of GABA-A receptor mediated inhibitory postsynaptic

* Corresponding author at: Department of Anesthesiology, Pharmacology & Therapeutics Faculty of Medicine, The University of British Columbia Vancouver, BC V6T 1Z3, Canada. Fax: +1 604 822 2290.
E-mail address: sastry@mail.ubc.ca (B.R. Sastry).

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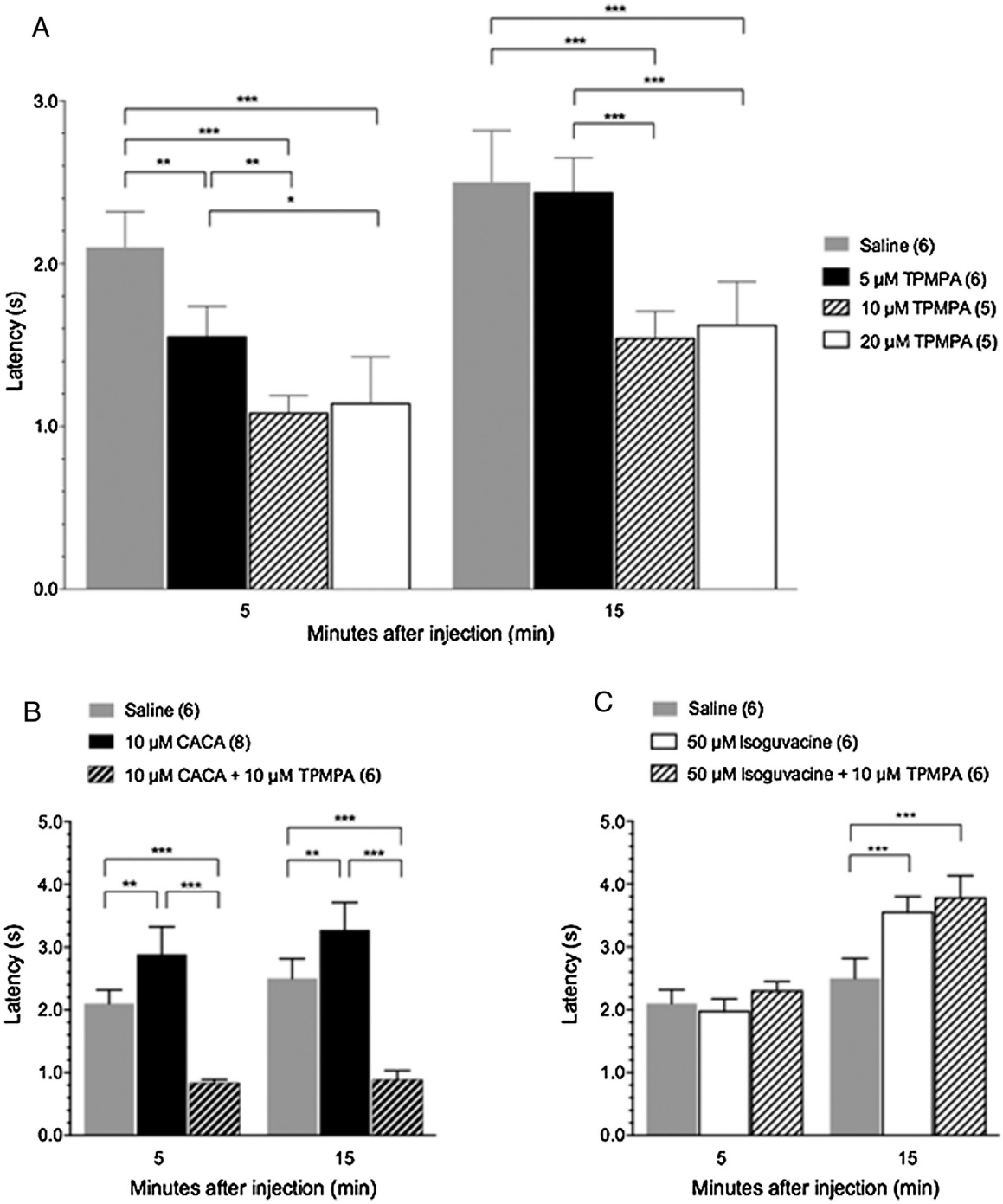

Fig. 1. Effect of TPMPA on the tail-flick response of Wistar rats. The tail-flick responses to a stimulus temperature of 51 °C were measured 5 and 15 min after intracisternal injection of: (A) 5–20 μM TPMPA, (B) 10 μM CACA with and without 10 μM TPMPA, and (C) 50 μM isoguvacine with and without 10 μM TPMPA. The number given in the legend inset represents the number of animals per group. Values represent mean ± SE. $^{*}p \leq 0.05$ $^{**}p \leq 0.01$ $^{***}p \leq 0.001$ (two-way ANOVA followed by the Sidak's multiple comparison test).

currents [43]. Exogenous introduction of the GABA-C receptors into cultured hippocampal neurons have been shown to suppress glutamate-induced hyperexcitability and delay neuronal cell death [4].

The flexibility that GABA-C receptors impart to synaptic inhibition, independently or via synergistic interactions with GABA-A receptors, can have enormous implications for the treatment and/or management of nociception and pain. Afferent nociceptive information is processed in the superficial spinal dorsal horn (SDH), Rexed's laminae I & II, and transferred to higher brain centers for conscious pain perception. At the spinal level, actions of GABA at axo-axonic synapses, cause presynaptic inhibition (PI) via primary afferent depolarization (PAD), which impedes further conduction of action potentials [8,9,33]. Modulation of PAD offers a potential mechanism for analgesia. The extent of PAD, when enhanced via combined effects of neighboring pain pathways or by actions of opioids and associated peptides, produces analgesic actions, by modulating evoked transmitter release and filtering nociceptive input [34,36,37]. GABA-B receptors, present at the axon terminals, seem to produce analgesic effects by regulating neurotransmitter