Evolving mechanisms of action of alverine citrate on phasic smooth muscle

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Abstract

We have investigated the mechanisms underlying the paradoxical ability of the antispasmodic, alverine, to enhance spontaneous activity in smooth muscles while suppressing evoked activity. The effects of alverine on spontaneous and induced contractile activity were examined in preliminary experiments with various smooth muscles. More detailed effects were also investigated by recording membrane potential, intracellular Ca2+ concentration ([Ca2+]i) and tension from single-bundle detrusor smooth muscle (DSM) of the guinea-pig urinary bladder. Alverine (10 microM) increased the frequency and amplitude of spontaneous action potentials, transient increases in [Ca2+]i and associated contractions. Alverine also decreased action potential rate of decay, suggesting inhibition of L-type Ca channel inactivation. Charybdotoxin (50 nM) but neither cyclopiazonic acid (10 microM) nor Bay K 8644 (10 microM) attenuated alverine-induced enhancement of spontaneous contractions. Alverine suppressed contractions produced by high K (40 mM) or ACh (10 microM), without affecting electrical responses and with little suppression of increases in [Ca2+]i. This feature was very similar to that of the effects of the Rho kinase inhibitor Y-27632 (10 microM). Alverine may increase Ca influx during action potentials due to inhibition of the inactivation of L-type Ca channels, but may also suppress evoked activity by inhibiting the sensitivity of contractile proteins to Ca2+. The proportional contribution of Ca-dependent and Ca-independent contractions in DSM may differ between spontaneous and evoked activity, necessitating further investigations into the interactions between these pathways for assessing the therapeutic potential of alverine to treat DSM dysfunction.

Citations (16)

References (20)

- ... The peak therapeutic effect is achieved within 0.5-1.5 hours, and the duration of action is 3-4 hours (76,77) . Preclinical pharmacological studies showed beneficial effects of alverine on intestinal motor function and sensitivity (79)(80)(81) . In their randomised, double-blinded, placebo-controlled trial using the Rome Committee's criteria, Wittmann et al. demonstrated significantly higher efficacy of alverine citrate and simethicone over placebo in alleviating abdominal pain and discomfort in IBS patients (82,83) . ...

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- ... Another hit not previously implicated in neuritogenesis was the smooth muscle relaxant alverine citrate, which promoted neurite outgrowth in our screen. Alverine citrates's mechanism of action is not well understood, but it has been proposed to antagonize 5HT1A receptors, and also regulate calcium influx and ROCK activity, potential routes for promoting neurite outgrowth (Coelho et al., 2001;Gupta et al., 2014;Hayase et al., 2007;Nikolic, 2002;Rojas et al., 2014). ...

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- ... Alverine citrate has been reported to exhibit a dual intestinal pharmacological activity with few systemic side effects [10]. It exerts a spasmolytic effect on smooth muscle cells that acts through basal and stimulated motility via a calcium-dependent and -independent inhibition of neuronal excitability [11] and through smooth muscle cell L-type Ca 2+ channels [12]. Additionally, alverine citrate has an antinociceptive effect associated with 5-HT 1A receptor antagonism, allowing it to modulate nociceptive response and visceral hypersensitivity [10]. ...

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- ... Preclinical pharmacological studies have shown the beneficial effects of alverine citrate on both intestinal motility and sensitivity (15)(16)(17)(18). As a selective 5-HT 1A receptor subtype antagonist, alverine citrate inhibits the rectal hypersensitivity induced by serotonin, a mediator involved in IBS hyperalgesia (17). ...

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