Synthetic Lapachol Derivatives Relax Guinea-Pig Ileum by Blockade of the Voltage-Gated Calcium Channels

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The present study was designed to further evaluate a possible spasmolytic activity of synthetic lapachol derivatives, norlapachol, *Ŭ*-norlapachone, *ƃ*-norlapachone and hydro-hydroxy-norlapachol (HH-norlapachol), on guinea-pig ileum. In guinea-pig ileum, except for norlapachol, all naphthoquinones inhibited the phasic contractions induced by carbachol or histamine. Even when the ileum was pre-contracted with KCl, carbachol or histamine, all naphthoquinones induced relaxation, suggesting that these naphthoquinones could be acting on the voltage-gated calcium channels (Ca_V). As the tonic component this contraction is maintained mainly by the opening of the Ca_V, we hypothesized that these naphthoquinones might be acting on these channels. This hypothesis was confirmed by the observation that norlapachol ($pD'_2 = 4.99$), *Ŭ*-norlapachone ($pD'_2 = 4.49$), *ƃ*-norlapachone ($pD'_2 = 6.33$), and HH-norlapachol ($pD'_2 = 4.53$) antagonized the contractions induced by $CaCl_2$ in depolarizing medium nominally without Ca^{2+}. As *ƃ*-norlapachone was the most potent we decided to continue the study of its action mechanism. The fact that this naphthoquinone has inhibited the tonic contractions induced by S-(-)-Bay K8644 [$EC_{50} = (1.6 \partial 0.30) \cdot 10^{-5}$ M] suggests that the Ca^{2+} channel involved belongs to the type L ($Ca_V1.2$). In addition, in the functional level, the spasmolytic effect of *ƃ*-norlapachone does not involve participation of free radicals, since its curve of relaxation was unchanged in the presence of glutathione, an antioxidant agent.

Key words: Synthetic Lapachol Derivatives, Guinea-Pig Ileum, Ca_V.