P41 Effect of γ-mangostin through the inhibition of 5-hydroxytryptamine$_{2A}$ receptors in 5-fluoro-α-methyltryptamine-induced head-twitch responses of mice

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Abstract: In order to discover new types of 5-hydroxytryptamine antagonists, we have devoted our attention to investigating naturally occurring compounds having anti-5HT activity *in vitro*. Recently, γ-mangostin [1,3,6,7-tetrahydroxy-2,8-bis(3-methyl-2-bytenyl)-9*H*-xanthen-9-one] from the fruit hull of *Garcinia mangostana* Linn has been shown to be a selective antagonist for 5-hydroxytryptamine$_{2A}$ receptors in smooth muscle and platelets. It is of interesting that γ-mangostin which does not have a nitrogen atom, posseses marked 5-HT$_{2A}$ receptor blocking activity. The present study was undertaken to investigate the effects of γ-mangostin on central 5-HT receptors by using animal behavioural models. Intracerebronventricular injection of γ-mangostin (10-40 nmol/mouse) inhibited 5-fluoro-α-methyltryptamin (5-FMT) (45 mg kg^{-1}, i.p.)-induced head-twitch response in mice in the presence or absence of citalopram (5-HT-uptake inhibitor). Neither the 5-FMT- nor the 8-hydroxy-2-(di-n-propylamino)tetralin (5-HT$_{1A}$-agonist)-induced 5-HT syndrome (head weaving and hindlimb abduction) was affected by γ -mangostin. The locomotor activity stimulated by 5-FMT through the activation of α_1-adrenoceptors did not alter in the presence of γ-mangostin. 5-HT-induced inositol phosphates accumulation in mouse brain slices was abolished by ketanserin. γ-Mangostin caused a concentration-dependent inhibition of the inositol phosphates accumulation and the binding of [^{3}H]-spiperone, a specific 5-HT$_{2A}$ receptor antagonist, to mouse brain membranes. Kinetic analysis of the [^{3}H]-spiperone binding revealed that γ-mangostin increased the K_d value without affecting the B_{max} value, indicating the mode of the competitive nature of the inhibition by γ-mangostin. These results suggest that γ-mangostin inhibits 5-FMT-induced head-twitch response in mice by blocking 5-HT$_{2A}$ receptors not by blocking the release of 5-HT from the central neurone. γ-Mangostin is a promising 5-HT$_{2A}$ receptors antagonist in the central nervous system.

References:

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