NOVEL LIPID DERIVATIVES OF SEROTONIN AND RESPIRATORY REGULATION

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Serotonin is an important neurotransmitter in the respiratory system. With regard to respiration, serotonin demonstrates a double effect: inhibition of the respiratory network at the brain level, but a stimulatory ventilatory effect at the peripheral chemoreceptors of the carotid body. This biogenic amine, however, does not cross the blood brain barrier, which confounds the interpretation of its ventilatory effects. We posed two main questions in the present study. First, could serotonin lipid derivatives, as opposed to serotonin proper, penetrate into the rat brain after intraperitoneal injection and would such compounds be active in ventilatory regulation? Second, how would the presumed ventilatory activity of lipid derivatives of serotonin depend on the length of fatty acid chains attached and the saturation of their carbon bonds? We addressed these question by examining four, de novo synthesized condensation products of serotonin and short- and long-chain fatty acids of varying saturation of carbon bonds: behenic (C22), oleic (C18), caprilic (C8) and caproic (C6) acids. In the biochemical part of the study, we assessed the recoverability of these compounds in the membrane and cytosolic brain tissue fractions obtained from rats euthanized 1, 3, 6, 9, and 12 hours after systemic administration of each compound. All compounds were injected i.p. in a dose of 50 mg/kg dissolved in 0.2 ml of DMSO. We used the techniques of thin layer chromatography (TLC) and UV/VIS spectrophotometry for the analysis. The results were negative. We did not observe any TLC bands at the level of the standards nor were there present any UV/VIS spectra corresponding to the calibration ones of the compounds studied. We further investigated the effects of these compounds, in the above-mentioned single dose, on the ventilatory responses to 12% and 8% hypoxia, balanced with nitrogen. The responses were studied in 12 awake Wistar rats and were taken before, as a control, and 60 min after each compound administration. Minute ventilation and its frequency and volume constituents were measured breath-by-breath using a Buxco Electronics (Wilmington, NC) rodent plethysmograph and software. Again, we found no appreciable effects of the compounds on chemical control of ventilation. We conclude that the novel lipid derivatives of serotonin studied do not penetrate through the blood brain-barrier and are devoid of functional ventilatory effects at the peripheral carotid body level. The biological barrier permeability of these compounds does not seem to relate with the length or saturation of the carbon fatty acid bonds.