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Memantine (a dual α7-nAChR/NMDAR antagonist) displays anti-angiogenic activity in human squamous cell lung cancer

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Cigarette smoking accounts for 85% of squamous cell lung cancer (SCC-L) in patients. Since SCC-L is a highly angiogenic tumor, anti-angiogenic therapies like Avastin have been investigated for the treatment of SCC-L. However, the drawback of these therapies has been the incidence of pulmonary hemorrhage and extensive hemoptysis in SCC-L patients. Nicotine, the addictive component of cigarettes, promotes angiogenesis in lung cancer via the α7-nicotinic acetylcholine receptor (α7-nAChR) subunit in human lung endothelial cells. Therefore, we conjectured that α7-nAChR-antagonists should display potent anti-angiogenic and antitumor activity in SCC-Ls. We observed that the α7-nAChR is robustly expressed on human microvascular endothelial cells of the lung (HMEC-Ls) and SCC-L associated endothelial cells (STACE). With this background in mind, we tested the anti-angiogenic activity of memantine (dual α7-nAChR/NMDAR antagonist) in SCC-Ls. Receptor binding assays have shown that the affinity of Memantine for α7-nAChR is greater than NMDAR. Here we show that memantine attenuates nicotine-induced angiogenesis in human microvascular endothelial cells of the lung (HMEC-Ls). Furthermore, the α7-nAChR antagonist memantine displayed potent anti-angiogenic activity in the chicken chorioallantoic membrane (CAM) model. Memantine is an FDA approved drug, used in clinical practice to treat mild-moderate Alzheimer's disease. It is well tolerated by patients and has a favorable side effect profile. Our studies are unique and innovative because they study, for the first time, the application of memantine in a non-neuronal disease, namely lung cancer.

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