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Angiotensin-Converting Enzyme Inhibitors Increase Substance P, Which Is Involved in Coughing, Inflammation, and Lung Cancer

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Angiotensin-converting enzyme inhibitors (ACEIs) are effective and safe drugs that have been used for many years to control high blood pressure. However, a systematic review and meta-analysis have reported the association between long-term (more than five years) use of ACEIs and the risk of lung cancer (LC). Of the 2,400 records reviewed, 13,061,226 patients met the inclusion criteria [1]. In line with this, it is known that the substance P (SP) peptide, after binding to the neurokinin-1 receptor (NK-1R), is involved in coughing [2], neurogenic inflammation (inflammation SP mediated) [3], and LC [4] and, therefore, could be considered mechanistically responsible for the risk of LC mediated by prolonged ACEIs use for the following reasons: ACE hydrolyze SP [5], while ACEIs can prevent the degradation of SP by blocking ACE [5], ACEIs increases SP levels and induces cough, in fact, ACEIs to cause coughing in 5-10% of patients [2]. SP also induces neurogenic inflammation [3] and LC [4]. ACE or kininase II is a peptidyl dipeptidase that splits C-terminal dipeptides of a large range of substrates, including angiotensin I, bradykinin, neurotensin, and SP [5]. It is a fact that ACE transforms the dormant decapeptide angiotensin I to the octapeptide angiotensin II. However, an important, lesser-known fact is that ECA also hydrolyzes SP, increasing its levels. In contrast, SP hydrolysis was completely blocked by the ACEI, captopril, in a concentration-dependent manner [5]. Thus, ACEI therapy increases SP levels and induces cough [2]. SP plasma levels are higher in subjects with cough [3] (including patients with ACEI treatment) and in patients with cancer compared to healthy subjects [3]. Previous studies indicate that long-term use of ACEIs may increase SP levels in lung tissue and mediate chronic neurogenic inflammation via SP [3, 6]. In addition, it is well known that chronic inflammation is the hallmark of cancer promotion. In fact, chronic inflammatory diseases are known to cause cancer (chronic pancreatitis can promote pancreatic cancer, chronic hepatitis can promote hepatocellular carcinoma, and inflammatory bowel disease can promote colon cancer) [6]. Similarly, persistent neurogenic inflammation mediated by SP can promote LC [3, 6]. Moreover, LC cells overexpress SP and NK-1R, and SP is a mitogen in LC cells [4]. In contrast, the drug aprepitant, a specific NK-1R antagonist, has an antitussive effect in patients with LC and refractory cough [7], as well as anti-inflammatory effects [3], and inhibits LC cell proliferation and induces apoptosis in LC cells [4]. In conclusion, ACEIs block ACE and increase SP levels, which, after binding to NK-1R, can cause coughing and neurogenic inflammation. Persistently elevated SP levels would cause chronic neurogenic inflammation, which, in the long term, could lead to the promotion of LC. Conversely, the use of the specific NK-1R antagonist drug, aprepitant, counteracts coughing, inflammation, and LC.

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