

Mechanisms of Action of Tea Polyphenols

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Tea polyphenols have attracted much attention as potential beneficial agents in a variety of human diseases. Human intervention studies are on the way where tea polyphenols are applied as beverages or as isolated compounds. Although promising experimental and clinical data demonstrate protective effects, still limited information is available on how these beneficial effects of tea polyphenols are mediated at the cellular level. For the elaboration of human studies and to understand their mode of action, the elucidation of molecular targets for tea polyphenols at the cellular level is inevitable. Owing to the scientific interest in beneficial properties of tea in cancer, neurological disorders, cardiovascular and other human diseases, a diverse spectrum of different cell types for molecular actions of tea polyphenols is involved. In addition, green and black tea that contain different biologically active compounds are consumed in distinct geographical regions. Evidence is accumulating that catechins in green tea as well as theaflavins and thearubigins from black tea are the substances responsible for the physiological effects of tea. The green tea catechin EGCG (epigallocatechin-3-gallate) is generally considered to be the biologically most active compound *in vitro*. The modification of the activity of various growth factors, transcription factors and protein kinases is a common mechanism involved in the molecular effects of tea polyphenols. By affecting the activity of receptor and intracellular signal transduction pathways, the major ingredients of green and black tea exert a variety of beneficial impacts in diverse cell types. Surprisingly, they frequently result in opposing effects. Whereas in fast-proliferating, activated cells (e.g. tumor cells) tea polyphenols inhibit the activity of intracellular signaling cascades (leading to cell cycle arrest and apoptosis), in primary, resting cells these pathways are activated. These apparently contradictory cellular effects provide the rationale for the potential use of tea polyphenols both against cancer and diseases without uncontrolled cell proliferation. In neurodegenerative disorders, besides their antioxidant effects, tea polyphenols interfere with the formation of toxic amyloids and even convert mature fibrils into non-toxic intermediates by direct binding to unfolded polypeptides or mature aggregates at the extracellular level.

Many human diseases are characterized by sustained inflammatory processes. Tea polyphenols exert direct and indirect antioxidant effects at the cellular level. These include direct scavenging of free radicals, chelating of metal ions, inhibition of cellular ROS generating enzymes and cytokine production at one hand and induction of intracellular free radical scavenging enzymes on the other hand. However, also the generation of reactive oxygen species by tea polyphenols was observed in a number of *in vitro* experiments. The extent of biological activity of tea polyphenols depends on their chemical structure. Overall, catechins and theaflavins containing a galloyl group at their 3 position proved to be physiologically most potent. The contribution of various other tea ingredients is less well understood. Many cell culture studies used much higher concentrations of tea polyphenols as can be achieved *in vivo* after tea consumption. Whereas this approach is able to detect many molecular targets at the cellular level, it also raises questions about the biological relevance of the observed effects for the *in vivo* situation.

Although an impressive progress has been made in recent years in the elucidation of molecular targets of tea polyphenols in diverse cell types, many questions still remain unresolved. Attempts to attribute functional effects *in vivo* to specific molecular signal transduction pathways affected at the cellular level are still at the beginning.