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In conclusion, evidence points in a new direction: that biochemical mediators, deriving from nerves in or around the patellar tendon or from the tendon tissue itself, may profoundly influence the nerves, blood vessels, and tenocytes in patellar tendon tissue. The findings furthermore suggest that these phenomena arise or increase in response to patellar tendinopathy, or even precede/elicit the condition, as they are only rarely or very moderately seen in normal patellar tendons. Thus, the ramifications of neuronal or non-neuronal biochemical mediators in patellar tendinopathy include effects on tendon tissue (tendinosis changes), vascular regulation, and/or pain signaling. Clinical use of this knowledge in the future might be of potentially high impact. If the model of biochemical pathogenesis/pathology in patellar tendinopathy proves to have some validity, it would mean that clinical management would aim

to modify the biochemical milieu, rather than just focusing on collagen repair. Eccentric training regimens and surgery would probably still have their uses, but researchers would be encouraged to pursue a pharmaceutical approach focused on reducing the irritant biochemical compounds in or around the tendon, if proven to be a causative factor in tendinopathy. This would actually mean that treatments might challenge the cause, rather than only the symptoms or consequences, of tendinopathy development.

However, first experimental studies must follow, to bring clarity to the actual role of the biochemical mediators produced in tendinosis tissue. Which substances inflict or enhance pain and tissue degeneration, and which substances promote tissue healing? Animal and cell culture models are currently being used to capture the dynamic events of tendinosis and answer these questions.

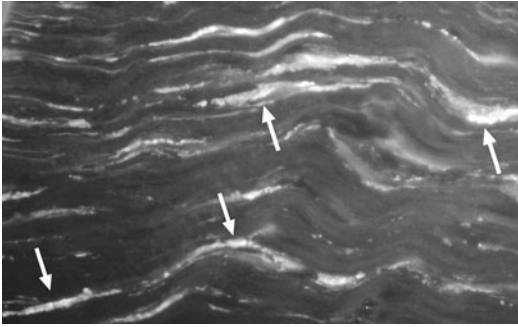
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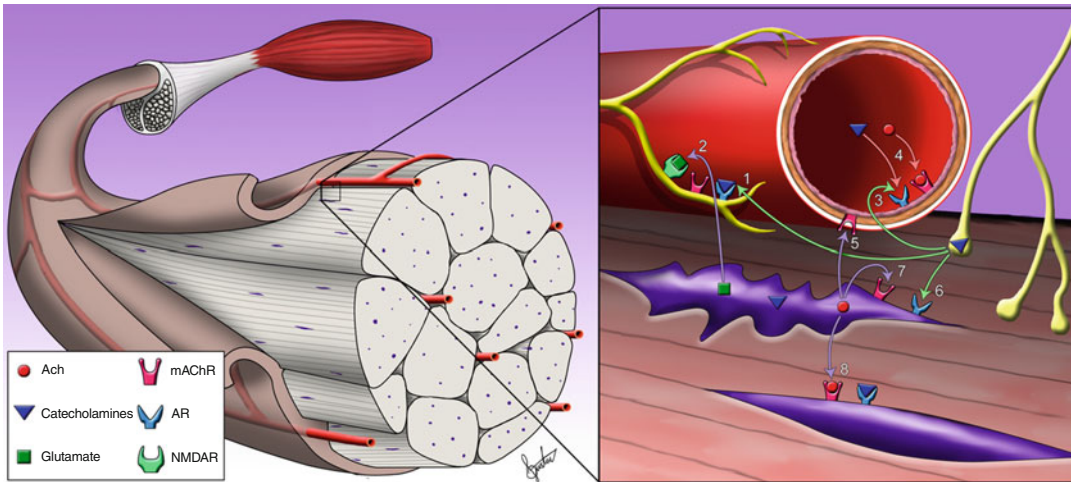
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**Fig. 15.1** Evidence of intratendinous ACh production. Tenocytes of patellar tendon tissue have been shown to harbor enzymes related to acetylcholine (ACh) production in tendinopathy patients. The ACh synthesizing enzyme choline acetyltransferase (ChAT), as well as its mRNA, have been found at intracellular locations. Furthermore, vesicular acetylcholine transporter (VACHT) – an enzyme that shuffles ACh from an intracellular site of synthesis into vesicles – has also been detected inside tenocytes as shown by this picture. Immunohistochemical staining (immunofluorescence method, TRITC) show specific immunoreactions inside the tenocytes, some indicated with *arrows*



**Fig. 15.2** Evidence of intratendinous catecholamine production. In-situ hybridization method shows reactions for tyrosine hydroxylase (TH) mRNA within some tenocytes (*filled arrow*) in patellar tendon tissue from a patient with tendinopathy. Other tenocytes (*unfilled arrows*) are negative in this regard. TH is the rate-limiting enzyme in the synthesis of catecholamines



**Fig. 15.3** The biochemical model for patellar tendinopathy. Schematic figure of patellar tendon tissue, showing the possible roles of biochemical mediators. The microscopic milieu is depicted in the frame to the right. Afferent sensory nerve fibers, here seen to the left in close association with a blood vessel, express muscarinic acetylcholine receptors (mAChR), *N*-methyl-d-aspartate receptors (NMDA R), and adrenergic receptors (AR). The sensory nerves are hereby susceptible to stimulation by the neurotransmitters acetylcholine (ACh) and glutamate, as well as by catecholamines. All these substances might thus theoretically affect pain signalling from the tendon. The adrenergic receptors might be influenced by catecholamines produced by neighboring efferent sympathetic nerves (1) “sympathetically maintained pain”). However, the mAChRs, the NMDA Rs, and the adrenergic receptors on the sensory nerves might also be stimulated by acetylcholine (ACh), glutamate, and catecholamines, respectively, which are produced by the tenocytes themselves (2) since these principal tendon cells have been shown to express biosynthetic enzymes for the substances in question when tendinopathy occurs. This phenomenon has been noted for the morphologically disfigured tenocytes that are frequently seen in tendinosis tissue (upper tenocyte in picture). Such tenocytes lack the slender, spindle-

shaped, appearance of normal tenocytes (lower tenocyte in picture). The efferent sympathetic nerves are furthermore likely to affect blood vessel regulation, via stimulation of adrenergic receptors in the blood vessel walls (3). Such receptors, alongside mAChRs in the blood vessel walls, are moreover expected to be stimulated by circulating catecholamines and ACh, respectively (4). A third possible source of catecholamines and ACh affecting blood vessel regulation is the tenocytes of the tendon tissue (5). The tenocytes, in addition to producing the signal substances in question, express adrenergic receptors and mAChRs, making them receptive to catecholaminergic and cholinergic effects (proliferation, changes in collagen production, and/or degeneration/apoptosis). The receptors on the tenocytes might, in the case of adrenergic receptors, be influenced by signal substances (catecholamines) produced by efferent nerves (6), or by signal substances (ACh and catecholamines) produced by the tenocytes themselves. In the latter case, autocrine (7) as well as paracrine (8) loops are suggested to occur. In summary, receptors on sensory nerves, blood vessels, and tenocytes in patellar tendons, might be affected by substances from efferent nerves (*green arrows*), the blood circulation (*red arrows*), and/or the tendon tissue itself (*purple arrows*) Copyright with artist: Gustav Andersson