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Effects mediated by α7 nicotinic receptors activation in Schwann cells: implication in peripheral nerve regeneration.

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Schwann cells (SCs) play a strategic role after peripheral nerve injury, driving axons regeneration and regulating local inflammation Recently we demonstrated the presence of α7 nicotinic acetylcholine receptors (nAChRs) in rat SCs. α7 nAChR is expressed in SCs after peripheral nerve axotomy and its expression is significantly enhanced after 24 h when sciatic nerve segments are cultured alone or in presence of the proinflammatory neuropeptide Bradykinin (BK). To clarify the role that α7 nAChRs play after peripheral axon damage, we investigated the signal transduction pathways triggered by receptor activation and the effects produced by their activation. Both ionotropic and metabotropic signaling pathway were analyzed by calcium imaging and Western blot analysis, respectively, following α7 nAChR activation by partial agonist ICH3. In addition, the expression of c-Jun was evaluated by immunocytochemistry and Western blot analysis. Finally, the cell migration was studied by a wound healing assay. Activation of α7 nAChRs by the selective partial agonist ICH3, did not induce calcium mobilization in SCs but positively modulated the metabotropic pathway involving PI3K/AKT/mTORC1 axis. Activation of the mTORC1 complex was confirmed by the up-regulated expression of its specific p-p70 $S6K^{Thr389}$ target. Moreover, the up-regulation of p-$AMPK^{Thr172}$, a negative regulator of myelination, was also observed concomitantly to an increased nuclear accumulation of the transcription factor c-Jun. Cell migration and morphology analyses demonstrate that α7 nAChR activation also promotes SCs migration. Moreover α7 nAChRs caused an upregulation of uPA, MMP2 and MMP9 activity and decrease the IL-6 production and release. These results demonstrate that ACh, probably released from regenerating axons or by SC themselves, may actively promote, through α7 nAChRs activation the Repair Schwann Cell phenotype and contribute to favour an anti-inflammatory microenvironment. These conditions are relevant to support the peripheral nerve regeneration.