

Cyclic nucleotide signaling and synaptic plasticity

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SAMENVATTING

Neuronen kunnen hun onderlinge connecties versterken om een verbeterde informatieoverdracht te bekomen. Dit kenmerk noemt men synaptische plasticiteit. Het is aangetoond dat synaptische plasticiteit van belang is bij cognitieve en affectieve processen, en in het bijzonder bij het vormen van geheugensporen. Deze plastische veranderingen worden bewerkstelligd door meerdere intracellulaire moleculaire paden die geactiveerd worden bij inkomende signalen in het neuron. In dit proefschrift hebben we ons gericht op een specifiek intracellulair pad, dat door activiteit van cyclisch nucleotiden wordt aangedreven. Het doel was na te gaan in welke mate verschillende cyclisch nucleotiden kunnen bijdragen tot gedragsveranderingen die synaptische plasticiteit als oorzaak hebben.

Met gedragsfarmacologische en electrofysiologische technieken, hebben we aangetoond dat twee types cyclisch nucleotiden, cGMP en cAMP, respectievelijk enkel in vroege of late fase van geheugenconsolidatie betrokken zijn, en dat ze serieel geschakeld zijn. cGMP heeft in een latere fase cAMP-gerelateerde signalen namelijk nodig om geheugensporen te vormen. Verder tonen onze bevindingen aan dat verhoogde activiteit van hetzelfde cAMP-gerelateerde pad in verschillende hersenstructuren tegengestelde affectieve gedragingen tot gevolg kunnen hebben. We stellen vervolgens ook nieuwe beloftevolle therapeutische strategieën voor aandoeningen die gekarakteriseerd worden door cognitieve symptomen. Daarvoor hebben we ons in eerste plaats gericht op phosphodiesterase remmers. Deze remmen de afbraak van cyclisch nucleotiden, en resulteren dus direct in een verhoogde activiteit van cAMP en/of cGMP. In deze these hebben we aangetoond dat het combineren van lage doseringen van verschillende types phosphodiesterase remmers mogelijk een interessant alternatief biedt om geheugenvorming te verbeteren. Tenslotte hebben we ook gekeken naar BDNF, een molecule waarvan de intracellulaire niveaus door activatie van cAMP en cGMP verhoogd worden. Onze resultaten wijzen op het potentieel van een selectieve agonist van de belangrijkste receptor van BDNF voor geheugenverbetering. In het algemeen dragen de bevindingen hier beschreven bij tot een beter begrip van de onderliggende processen van geheugenvorming en zullen ze de ontwikkeling van verbeterde behandelingen voor cognitieve stoornissen faciliteren.

SUMMARY

Neurons have the fascinating ability to strengthen their connections to achieve enhanced information transmission. This feature is known as synaptic plasticity. It has been demonstrated that synaptic plasticity is of vital importance in cognitive and affective processes, and in particular in the formation of memory. The synaptic changes are attained by multiple intracellular molecular pathways that are activated in the neuron by incoming signals. In this thesis we have focused on a specific intracellular pathway which is centered around the activity of cyclic nucleotides. Our aim was to evaluate to what extent different cyclic nucleotides contribute to behavioral changes resulting from synaptic plasticity.

Using behavioral and electrophysiological techniques, we demonstrated that two types of cyclic nucleotides, i.e. cGMP and cAMP, are involved in respectively the early or late phase of memory consolidation, and that they act in sequence. That is, cGMP requires cAMP-related signals in a later phase after learning to form a stable memory trace. In addition, our findings show that enhancing signaling in the same cAMP-related pathway can result in different behavioral outcomes depending on the brain structure targeted. Furthermore, we have proposed novel promising therapeutic strategies for diseases associated with cognitive symptoms. Firstly, we have focused on phosphodiesterase inhibitors. These inhibit the breakdown of cyclic nucleotides and thus result directly in an augmentation of cAMP and/or cGMP. In this thesis we have demonstrated that combining low dosages of different types of phosphodiesterase inhibitors potentially represent an interesting alternative to enhance memory formation. Secondly, we have focused on BDNF, a neurotrophin of which the intracellular levels are increased in response to cyclic nucleotide signaling. Our results point to the potential of a selective agonist of the most important receptor of BDNF in cognition enhancement. In general, our findings contribute to a better understanding of the underlying processes of memory formation, and will facilitate the development of novel and improved treatments for cognitive dysfunctions.

