Institutionen för fysiologi och farmakologi

Centrum för molekylär medicin

Serotonin in Emotional Memory Processes: Neuropharmacological Studies with Emphasis on Depression

AKADEMISK AVHANDLING
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av
Therese M. Eriksson
MSc

Huvudhandledare:
Docent Per Svenningsson
Karolinska Institutet
Institutionen för klinisk neurovetenskap
Centrum för molekylär medicin
Enheten för translationell neurofarmakologi

Bihandledare:
Professor Sven Ove Ögren
Karolinska Institutet
Institutionen för neurovetenskap
Enheten för beteendeneurovetenskap

Fakultetsopponent:
Professor John F. Cryan
University College Cork, Cork, Ireland
Department of Anatomy and Neuroscience

Betygsnämnd:
Professor Hans Ågren
Sahlgrenska akademin, Göteborgs universitet
Institutionen för neurovetenskap och fysiologi
Enheten för psykiatri och neurokemi

Professor Ernst Brodin
Karolinska Institutet
Institutionen för fysiologi och farmakologi
Enheten för farmakologisk smärtforskning

Professor Marianne Schultzberg
Karolinska Institutet
Institutionen för neurobiologi,
vårdvetenskap och samhälle
Enheten för neurodegeneration

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ABSTRACT

Cognitive dysfunctions are common in neuropsychiatric disorders including Major Depressive Disorder, but are difficult to normalize by antidepressant therapies and contribute to reduced functional improvement. Cognitive impairments include alterations of emotional memory processes that are early targeted by antidepressant therapies, including Selective Serotonin Reuptake Inhibitors (SSRIs). This thesis focused on serotonin neurotransmission in modulation of emotional and cognitive processes. A combination of neuropharmacological methods was used to study possible neurobiological mechanisms underlying alterations of memory function in normal rodent strains and two genetic models of depression, *i.e.* the multigenetic Flinders Sensitive Line (FSL) of rats and the p11 knockout (p11 KO) mice. Pharmacological treatments were used to evaluate responses to acute, chronic and intrahippocampal administration of antidepressants and serotonergic receptor (5-HTR) subtype-specific ligands. Emotional memory function was assessed in the Passive Avoidance task for aversive contextual learning and memory, which involves hippocampal mechanisms. Additional studies were made for Novel Object Recognition memory performance and autonomic measures with Auditory Fear Conditioning. Depression- and anxiety-like behaviors and sensorimotor function were studied in combination with biochemical and histological experiments, Magnetic Resonance Spectroscopy, enzyme-based Micro-Electrode Assay of L-glutamate kinetics and Adeno-Associated Viral vector-mediated gene transfer.

Evaluation of the role of 5-HTR subtypes in emotional memory processes revealed interactions and opposing roles between the extensively characterized 5-HT_{1A}R and the most recently discovered 5-HT_7R subtype. Stimulation of 5-HT_{1A}Rs impaired memory performance, both after systemic and intrahippocampal application, indicating a specific involvement of hippocampal 5-HT_{1A}Rs in acquisition of the Passive Avoidance task. In contrast, aversive learning was facilitated by stimulation of 5-HT_7Rs through indirect agonist stimulation, endogenous 5-HT or elevated 5-HT levels by an SSRI. Agonist stimulation of 5-HT_{1B}Rs impaired memory performance, whereas 5-HT_{1B}R antagonism improved memory function in control mice, via interactions with cholinergic and glutamatergic neurotransmission.

Impairments of long-term emotional memory performance were found in two animal models with genetic predisposition for depression-like symptoms, the FSL rats and p11 KO mice. Memory dysfunctions in FSL rats were reversed by three types of treatments increasing Arc mRNA transcription: (1) chronic antidepressant food-administration of an SSRI, and acute (2) 5-HT_{1A}R antagonist or (3) 5-HT_4R agonist via the mitogen-activated protein kinase pathway. In contrast, a tricyclic antidepressant regimen, which increased brain-derived neurotrophic factor signaling, impaired memory function. In p11 KO mice, preserved short- but impaired long-term memory function was accompanied by reduced hippocampal inhibitory glutamine/gamma-aminobutyric acid (GABA) neurochemical concentrations and an atypical stimulatory 5-HT_{1B}R agonist behavioral response, reversible by hippocampal p11 gene transfer. 5-HT_{1B}R agonism also increased evoked L-glutamate release in the dentate gyrus and CA1 subregions and hippocampal glutamate receptor phosphorylation in p11 KO mice.

In conclusion, these studies indicate pharmacological restorations of emotional memory deficits in genetic rat and mouse models of depression, suggesting potential relevance and validity for use as models for aspects of cognitive dysfunction endophenotypes. The identification of molecular nodal points for 5-HTR-mediated memory enhancement could provide targets for antidepressants and procognitive therapies improving neurotransmission in functional circuitries regulating emotional and cognitive processes.

Karolinska Institutet, Stockholm, Sweden

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