Umeå University Medical Dissertations
New Series No 1026 – ISSN 0346-6612 – ISBN 91-7264-073-1

Tolerance and antagonism to allopregnanolone effects in the rat CNS

av

Sahruh Turkmen

Akademisk avhandling

som med vederbörligt tillstånd av rektorsämbetet vid Umeå universitet för avläggande av filosofie doktorsexamen
framläggs till offentligt försvar i Betula salen, by. 6M,
fredagen den 15 September 2006, kl.09.00.
Avhandlingen kommer att försvaras på engelska.

Fakultetsopponent: Prof. Agneta Nordberg, Karolinska Institutet, Dept. Neurotec and Mol. Neuropharmacol., Geriatriska kliniken, Karolinska Universitetssjukhuset Huddinge, Stockhom.

Department of Clinical Science, Obstetrics & Gynecology
Umeå University
Umeå 2006

New Series No 1026 – ISSN 0346-6612 – ISBN 91-7264-073-1

Tolerance and antagonism to allopregnanolone effects in the rat CNS

Sahruh Turkmen
Clinical Science, Obstetrics&Gynecology, Umeå University, SE-901 85 Umeå, Sweden.

ABSTRACT

Many studies have suggested a relation between sex steroids and negative mental and mood changes in women. Allopregnanolone, a potent endogenous ligand of the GABA-A receptor and a metabolite of progesterone, is one of the most accused neuroactive steroids. Variations in the levels of neuroactive steroids that influence the activity of the GABA-A receptor causes a vulnerability to mental and emotional pathology. In women, there are physiological conditions when the allopregnanolone production increases acutely (e.g. stress) or chronically (e.g. menstrual cycle, pregnancy), thus exposing the GABA-A receptor to high allopregnanolone concentrations. In such conditions, tolerance against allopregnanolone probably develops. We have evaluated the 3β-hydroxy pregnane steroid UC1011 as a functional antagonist to allopregnanolone-induced negative effects in rats. In vivo we used the Morris Water Maze (MWM) test of learning, and in vitro we studied chloride ion uptake into cortical and hippocampal membrane preparations. The steroid UC1011 decreases the allopregnanolone induced learning impairment in the MWM, and the increase in chloride ion uptake induced by allopregnanolone. To detect if chronic tolerance develops to an allopregnanolone induced condition, male rats were pretreated with allopregnanolone injections for 3, or 7 days. Thereafter these rats were tested in the Morris water maze for 5 days, and compared with relevant controls. Rats with 7 days allopregnanolone pretreatment had an improved performance compared with the acutely allopregnanolone exposed group, reflecting chronic tolerance development. To study the GABA-A receptor changes in acute allopregnanolone tolerance, we used the silent second (SS) anesthesia threshold method. At acute tolerance, 90 min of anaesthesia, the abundance of the GABA-A receptor α_4 subunit and expression of the α_4 subunit mRNA in the thalamus ventral-posteriomedial (VPM) nucleus were decreased. There was also a significant negative correlation between the increase in allopregnanolone dose needed for maintenance of anesthesia and the α_4 mRNA in the VPM nucleus. We also investigated if allopregnanolone tolerance was still present one or two days after the end of the anesthesia induced acute tolerance. Tolerance persisted to one day, but not two days, after the treatment and the α_4 subunit mRNA expression in the VPM nucleus was negatively related to the allopregnanolone doses needed after one day.

In conclusion, the current thesis show that the substance UC1011 can decrease the allopregnanolone induced negative effects in the water maze test. Chronic allopregnanolone tolerance can develop to allopregnanolone effects. Allopregnanolone tolerance persists one day after the induction of acute allopregnanolone tolerance. The GABA-A receptor α4 subunit in thalamus might be involved in the acute allopregnanolone tolerance development and persistence.

Key words: Allopregnanolone, GABA-A receptor, UC1011, Spatial memory, mRNA Morris water maze, Tolerance, Silent second.