

## Sex-related differences in cerebral A<sub>1</sub> adenosine receptor availability in the human brain

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### Introduction:

Sex differences have been reported in terms of sleep duration, sleep efficiency, and sleep phases. Adenosine and its cerebral receptors, A<sub>1</sub> adenosine receptor (A<sub>1</sub>AR) and A<sub>2A</sub> adenosine receptor (A<sub>2A</sub>AR), play an important role in homeostatic sleep-wake regulation. During wakefulness adenosine concentration increases, whereas it decreases during sleep. We investigated sex differences in the adenosine A<sub>1</sub>AR availability in human volunteers.

### Methods:

We used the radioligand [<sup>18</sup>F]CPFPX combined with positron emission tomography to quantify brain A<sub>1</sub>AR availability in 50 volunteers (20 female, 30 male, 28 ± 5 years). Following a one-week ambulatory sleep satiation protocol (9 hours time in bed, TIB), scans were performed under well-rested conditions after at least three nights in the sleep lab with 8 hours TIB. The A<sub>1</sub>AR availability was estimated in terms of the [<sup>18</sup>F]CPFPX binding potential ( $BP_{ND}$ ) via the Logan's reference tissue model ( $t^* = 30$  min) based on average  $k_2'$ , resulting from the simplified reference tissue model. The cerebellum was used as a reference region. With independent t-tests we compared  $BP_{ND}$  between males and females.

### Results:

Grey matter was subdivided into 12 regions.  $BP_{ND}$  was regionally 12-29 % higher in females than in males. Notably, in females,  $BP_{ND}$  was significantly higher in all brain regions indicating higher A<sub>1</sub>AR availability in females. The differences in  $BP_{ND}$  were particularly noticeable in regions which belong to the limbic system or are closely associated with it, such as anterior cingulum ( $0.57 \pm 0.11$  in females,  $0.45 \pm 0.11$  in males), hippocampus ( $0.55 \pm 0.08$  in females,  $0.43 \pm 0.11$  in males), and amygdala ( $0.51 \pm 0.10$  in females,  $0.41 \pm 0.11$  in males).

### Conclusion:

Females compared to males have a higher A<sub>1</sub>AR availability in the human brain already under well-rested conditions, which could explain the known sex differences in habitual sleep duration.

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