Evidence for reduced tonic levels of GABA in the hippocampus of an animal model of ADHD, the spontaneously hypertensive rat

Toni-Lee Sterley, Fleur M. Howells, Vivienne A. Russell

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Abstract

Recent studies have investigated the role of γ-aminobutyric acid (GABA) in the behavioural symptoms of attention-deficit/hyperactivity disorder (ADHD), specifically in behavioural disinhibition. Spontaneously hypertensive rats (SHR) are widely accepted as an animal model of ADHD, displaying core symptoms of the disorder. Using an in vitro superfusion technique, we have shown that glutamate-stimulated release of radio-actively labelled norepinephrine ([3H]NE) from prefrontal cortex and hippocampal slices is greater in SHR than in their normotensive control strain, Wistar-Kyoto rats (WKY), and/or a standard control strain, Sprague-Dawley rats (SD). In the present study, we investigated how the level of extracellular (tonic) GABA affects release of [3H]NE in hippocampal slices of male and female SHR, WKY and SD rats, in response to 3 glutamate stimulations (S1, S2, and S3). The hippocampal slices were prelabelled with [3H]NE and superfused with buffer containing 0 μM, 1 μM, 10 μM, or 100 μM GABA. Three consecutive glutamate stimulations were achieved by exposing slices to 3 pulses of glutamate (1 mM), each separated by 10 min. Increasing tonic levels of GABA increased basal and stimulated release of [3H]NE in all strains. When GABA was omitted from the superfusion buffer used to perfuse SHR hippocampal slices, but present at 100 μM in the buffer used to perfuse WKY and SD hippocampal slices, glutamate-stimulated release of [3H]NE was similar in all three strains. In these conditions, the decrease in [3H]NE release from S1 to S2 and S3 was also similar in all three strains. These findings suggest that extracellular concentrations of GABA may be reduced in SHR hippocampus, in vivo, compared to WKY and SD. An underlying defect in GABA function may be at the root of the dysfunction in catecholamine transmission noted in SHR, and may underlie their ADHD-like behaviours.