Methylphenidate administration during adolescence produces long-term effects in adult rat brain: a 1H MRS in vivo study

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Introduction

Administration of methylphenidate (MPH, Ritalin ®) to children affected by attention deficit hyperactivity disorder (ADHD) is an elective therapy, but raises concerns for public health, due to possible persistent neurobehavioral alterations. In an intolerance-to-delay operant task, MPH-treated adolescent animals showed a less marked shift from a large-but-delayed to a small-but-immediate reward, suggesting that a MPH therapy is able to reduce the level of impulsivity, compared to controls[1]. Aim of this study was to assess by 1H MRS whether MPH exposure of rats during adolescence also induced long-term biochemical changes observable during adulthood.

Materials and Methods

Wistar adolescent rats (30- to 44-day-old) were treated with MPH (2 mg/kg per die) or saline (SAL) for 15 days and tested at adulthood in drug-free state for a) potential carry-over effects on levels of impulsivity and b) possible NMR-detectable biochemical alterations. In order to test their impulsivity, animals were tested in the intolerance-to-delay protocol, involving choice between a small immediate or a larger delayed reward[1]. MR examinations were performed on a VARIAN Inova MRI/MRS system operating at 4.7 T, by using a volume coil as transmitter and a surface coil constructed for rat head as receiver (RAPID Biomedical). Multislice T2-weighted (TR/TE = 3000/70 ms, ns = 2, slice thickness 1 mm, matrix 128 x 256) sagittal images were acquired to localise the regions of interest. Single voxel localised 1H MR spectra (PRESS, TR/TE = 4000/23 ms, ns = 256) were collected from: prefrontal cortex (PFC), 58 μl; dorsal striatum (STR), 56 μl and nucleus accumbens (NAcc), 21 μl, as shown in Fig.1. Spectra were analysed by using LCModel fitting program[2]. The unsuppressed water signal was used for metabolite quantification. Statistical analysis was performed by using randomised block ANOVA. The litter was the blocking factor. Pre-treatment was a within litter factor.

Results and Discussion

The impulsivity test clearly demonstrated reduced impulsivity in MPH-exposed rats, when compared with their SAL-exposed siblings. A typical in vivo 1H MR spectrum obtained in the prefrontal cortex of rat brain is shown in Fig. 2. Quantitative metabolite analyses are summarised in Table 1. Creatine appeared up-regulated and phosphocreatine down-regulated in the PFC of MPH-exposed rats suggesting altered cortical function. Interestingly, total creatine and taurine, reputed to be involved in cell activation, were up-regulated in STR and conversely down-regulated in NAcc of MPH-exposed rats. We suggest that the influence of these two areas on behavioral output was modulated accordingly. Based on the functional role thought to be played by STR and NAcc, MPH-exposed animals may be suggested to be more prone to elaborate novel behavioral habits, in order to cope with delayed reinforcement, and to be less instinctively attracted by the immediate reward.

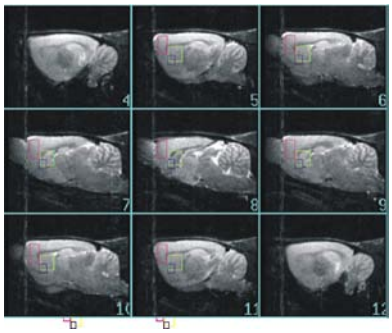

Fig. 1 Typical T2-weighted sagittal images obtained from a MPH pre-exposed rat brain.
ROIs: Prefrontal Cortex (PFC)
Dorsal Striatum (STR)
Nucleus Accumbens (NAcc)

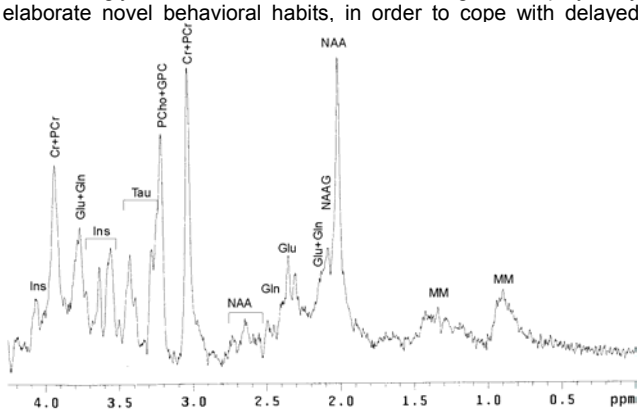

Fig. 2 Example of spectrum obtained from the PFC of the brain of a MPH pre-exposed rat.

TABLE 1
Metabolic parameters in PFC, STR NAcc

	Saline pre-exposed	MPH pre-exposed	Saline pre-exposed	MPH pre-exposed	Saline pre-exposed	MPH pre-exposed
t NAA	0.95±0.06	1.03±0.09	1.25±0.08	1.35±0.04	1.55±0.05	1.35±0.06 *
NAA	0.83±0.05	0.89±0.08	1.09±0.07	1.22±0.05	1.31±0.06	1.12±0.07
t Cho	0.19±0.02	0.18±0.02	0.35±0.02	0.40±0.01 *	0.41±0.02	0.39±0.03
tCr	1.20±0.04	1.25±0.08	1.42±0.05	1.53±0.04 *	1.75±0.06	1.50±0.07 *
Cr	0.6±0.1	0.46±0.06 *	0.6±0.2	0.58±0.2	0.7±0.3	0.58±0.2
PCr	0.62±0.07	0.8±0.1 *	0.8±0.2	0.95±0.2	1.1±0.3	0.91±0.3
Glx	2.3±0.2	2.3±0.1	2.7±0.2	2.6±0.2	2.85±0.09	3.0±0.2
Gln	1.0±0.2	0.96±0.08	1.03±0.09	0.99±0.09	1.12±0.06	1.30±0.08 *
Glu	1.4±0.1	1.39±0.09	1.65±0.09	1.77±0.03	1.73±0.09	1.8±0.2
Tau	0.95±0.07	1.00±0.07	1.25±0.09	1.47±0.07 *	1.4±0.1	1.05±0.08 *
Ino	0.99±0.09	1.04±0.08	1.24±0.06	1.38±0.04	1.06±0.05	1.0±0.1

(*) $p < .05$ when compared to saline pre-exposed.

Conclusions

In summary, our data indicate that adolescent MPH exposure produces long-term functional changes in reward-related circuits. These enduring MRS-detectable biochemical modifications may account for the finding of reduced basal behavioral impulsivity in the adult rat.

References

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2. S. W. Provencher, Magn Reson Med 30, 672, 1993.