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THE PREFRONTAL CORTEX BLOOD SUPPLY IN *CERCOPITHECUS AETHIOPS* – NEW APPROACH TO THE NON-PRIMATE MODEL OF SCHIZOPHRENIA

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Establishing a non – human prefrontal cortex schizophrenia studying model has been a subject of interest in the past decade. Authors intended to contribute to this model with the study of the blood supply of the prefrontal cortex of Cercopithecus Aethiops. Hence, we have microdissected 24 formaldehyde – ethanol fixed brains (48 hemispheres) of adult Cercopithecus Aethiops in order to reveal the origin, calibers and pathway of the prefrontal branches. On 22 of 24 brains, prefrontal rami originated from the dorsal terminal branch of the middle cerebral artery by a common arterial trunk, while on two brains they occured as "early cortical branches" from the terminal part of the middle cerebral artery. The average caliber of the common trunk on both sides was approximately 500 μm, or about a half of the "mother artery", without significant left – right asymmetries. The adequacy of the vascular pattern of the prefrontal cortex of the Cercopithecus Aethiops for future experimental investigations of schizophrenia has also been discussed.

Key words: Prefrontal cortex, blood supply, Cercopithecus Aethiops, schizophrenia, non - human primates model

INTRODUCTION

Symptoms of Prefrontal Cortex (PFC) Dysfunction accompany many mental disorders, including schizophrenia, Korsakoff's amnesia, and attention-deficit hyperactivity disorder (ADHD). Research in non-human primates indicates that the primary function of the PFC is to guide behavior by working memory. In this context, the impulsive, disorganized, and distracted behavior of patients with schizophrenia and ADHD can be viewed as an inability to regulate responses by internal representations from memory (Arnsten *et al*., 1996). Furthermore, a recent clinical study revealed a disturbed blood perfusion in the PFC while schizophrenia suffering patients were performing specific tests (Brunet *et al*., 2003).

We have performed this study with the aim to contribute to the establishment of a reliable animal model of schizophrenic brain, which involves detailed information about blood supply of PFC.

MATERIAL AND METHOD

The investigation was performed on brains of 24 healthy, non – infected, decapitated male adult Cercopithecus Aethiops, obtained from the Institute of Immunology – "Torlak" after sacrificing. The sacrifice process by application of Kethonal® (Galenika, Beograd), was entirely congruent to the National Guidelines about Experiments on Laboratory Animals. The head and neck complex was immediately after decapitation injected with liquid rubber (Latex ®) under pressure of 140 mmHg, through a baby system for catheterization, placed in the common carotid artery, and preserved in 10 % solution of formaldehyde. Within one – month period, fixed brains were removed out of the cranial cavity and kept in a form of "floating fixation" (tied to the carrier after the submersion in order to prevent the deformation of the brain) in a solution mixture of 4 % formaldehyde and 70 % ethanol for one month. Finally fixed brains underwent a microdissection under stereo magnifying glass. The brain tissue of the superior temporal gyrus was removed in order to expose the insular segment of the middle cerebral artery (M_2) for exploration. The number, origin, diameters of the prefrontal branches, and middle cerebral artery/prefrontal branches caliber ratio on each hemisphere were revealed. The diameters of the blood vessels were obtained by calibrated ocular micrometer with a measurement error of 20 μm, at the very site of branching.

In statistical evaluation, we used usual descriptive statistics (central tendency measures: mean and mode, standard deviation - SD, minimum, maximum), while interhemisferic differences were verified by Student's t-test for paired samples. The testing was performed on 95% probability level.

RESULTS

In 22 out of 24 brains, prefrontal branches (PFB) originated in the insular segment, form the dorsal terminal trunk of the middle cerebral artery (MCA). Their number was constant, two branches per hemisphere were revealed, mostly originating from a common trunk. From the branching point of the common trunk, one artery was directed dorso – laterally (dorsal branch), between the anterior subcentral sulcus and superior ramus of the arcuate sulcus, then curving frontally, irrigating the area rostral and dorsal to the principal sulcus. The other branch runs almost horizontally (horizontal branch), parallel to the principal sulcus, supplying fronto – orbital part of the frontal lobe, and prefrontal cortex ventral to the principal sulcus. On one specimen prefrontal arteries occurred from a common trunk with the central artery (fig. 1). On two brains they branched directly from the terminal part of MCA. Ranges and means are shown in Table 1. No left – right asymmetry in appearance or in number of branches was obtained on our specimens. In order to make an adequate comparison with human prefrontal arteries, we have calculated scores between the common trunk and its daughter branches and parent trunk of MCA, and their distribution was shown on Tables 2 and 3. The trend of left – right asymmetry absence remained in the evaluated scores, as well.

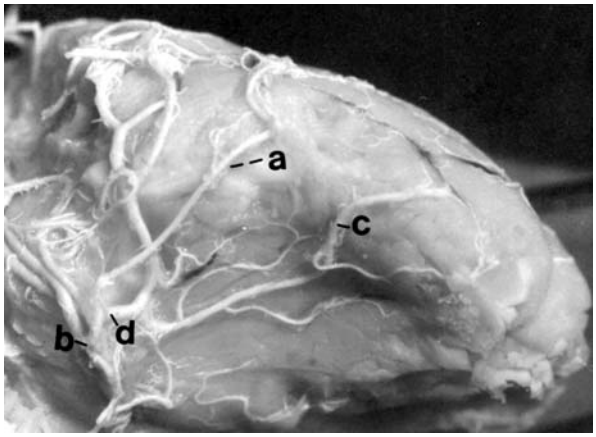

Figure 1. A standard pattern of prefrontal arteries from an unusual initial common trunk. a. – dorsal branch b – a common trunk for prefrontal arteries and central artery (running through central sulcus) c – horizontal branch d – central artery

Table 1. Mean values (± SD) and ranges of the obtained common trunk diameters (in micrometers)

Values	Left hemisphere	Right hemisphere
Minimum	320	380
Maximum	660	700
Mean ± SD	500 ± 110	490 ± 90

Left – right differences: t – test = 0.373, df = 23 p > 0.05

Table 2. Prefrontal common trunk/MCA parent trunk scores

Values	Left hemisphere	Right hemisphere
Minimum	0.42	0.43
Maximum	0.67	0.70
Mean ± SD	0.52 ± 0.06	0.51 ± 0.05

Left – right differences: t – test = 0.369, df = 23 p > 0.05

Table 3. Daughter branches/MCA parent trunk scores

Values	Left hemisphere	Right hemisphere
Minimum	0.27	0.26
Maximum	0.38	0.41
Mean ± SD	0.31 ± 0.05	0.30 ± 0.04

Left – right differences: t – test = 1.427, df = 47, p > 0.05

DISCUSSION

In this paper the authors intended to contribute to the establishment of a reliable non-human primate model of schizophrenia investigating the blood supply of the prefrontal region on the brains of Cercopithecus Aethiops (African Green Monkey).

Non – human primate brain model, particularly prefrontal cortex, has been used in various experimental researches of the roots in the genesis of some psychopathologic phenomena, such as perseveration, recognizing objects and space orientation inability, or brain distractibility (Javitt *et al*., 1995; Keefe *et al*., 1995; Freedman *et al*., 1998. Gaymard *et al*., 2003). Amygdaloid complexes of non-human primates, as well, seemed to be adequate for exploration of the dysfunction of amygdaloid complexes. This model contributes to the investigation of emotional changes, seen commonly in humans, which accompany certain neurological disorders, including dementia and schizophrenia (Aggleton, 1993). Furthermore, histological studies demonstrated cellular destruction in experimentally induced schizophrenia – like conditions (Guidotti *et al*., 2000). Finally, the prefrontal cortex in non - human primates shows similar affinity for neuroleptics as in humans, including side effects very much alike those obtained in the human population (Linn *et al*., 2001).

Recent studies report that impairment of the prefrontal cortex was involved in generating many neuropsychiatric illnesses equally among children and adults, such as schizophrenia, depression, obsessive – compulsive disorder, attention deficit hyperactivity disorder. Head trauma (Brunet *et al*., 2003; Ernst *et al*., 2003, Lacerda *et al*., 2003, Manly *et al*, 2003; Videbech *et al*., 2003) and compromised blood perfusion in the mentioned disorders were a certain kind of “file rouge” for this group of illnesses.

A suitable model would not be complete without a comparison between prefrontal cortex vascular patterns obtained in humans and in Cercopithecus Aethiops. First, prefrontal arteries on brains of both species of primates are originating from the dorsal terminal trunk of the middle cerebral artery, seldom branching from the initial segment of MCA, equally in humans and African Green Monkeys. Second, the most frequent finding is the presence of two arteries on both hemispheres in humans, while on Cercopithecus brains two branches are arising from the common arterial trunk, although the number of arteries varied more in humans – from one to six (Umansky *et al*., 1984; Marinkovic *et al*., 2002). It seems that the study of the dorsal branch is of higher importance, concerning the vascularly induced impairments in its supplying area equivalent in humans (Thomas *et al*., 2003). The appearance of prefrontal branches from the terminal part of the MCA was also described on human brains as “early cortical branching” (Gibo *et al*., 1981).

In conclusion, the prefrontal cortex of Cercopihtecus Aethiops is supplied by the branches of the middle cerebral artery, originating from the dorsal terminal branches, firstly as a common trunk, which branches shortly after on two branches: one, dorsal, that supplies parts of the prefrontal cortex dorsal to the principal sulcus, and the other, horizontal, which irrigates the area ventrally to the

principal groove. The described vascular pattern seems to be appropriate for incoming experimental researches on non – human primate model of not only schizophrenia, but also other neuropsychiatric disorders.

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VASKULARIZACIJA PREFRONTALNE KORE MAJMUNA *CERCOPITHECUS AETHIOPS* – NOVI PRISTUP MODELU ŠIZOFRENIJE

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SADRŽAJ

U poslednjoj dekadi prošloga veka poraslo je interesovanje za izradu modela ne-primatskog prefrontalnog koretksa u svrhu istraživanja promena nastalih u shizofreniji. Želja autora je bila da doprinesu ovom modelu istraživanjem vaskularizacije prefrontalnog korteksa zelenog afričkog majmuna (*Cercopithecus Aethiops*). U tu svrhu, izvršena je mikrodiskecija 24, formalin - etanol metodom fiksirana mozga, odraslih Cerkopitekusa, u cilju da određivanja porekla, promera i pravca prostiranja prefrontalnih grana. Na 22 od 24 mozga, dve prefrotnalne grane su polazile iz dorzalnog završnog stabla *a. cerebri mediae* (ACM) u formi zajedničkog stabla, dok su na dva mozga one poticale iz završnog dela ACM, u vidu „ranih kortikalnih grana". Prosečan promer grana na obe hemisfere iznosio je oko 500 μm, što je iznosilo oko polovinu „majke arterije", bez levo – desnih asimetrija po bilo kom pitanju.