REVIEW

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Experimental cerebral hemispherectomy in rodent models. A systematic review of current literature

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Cerebral hemispherectomy is a neurosurgical procedure that involves surgically removing one hemisphere of the brain, used as a therapeutic option in severe cases of intractable epilepsy. Several animal models have contributed to our understanding of the underlying neuromechanisms. The review was based on a PubMed search using the terms "hemispherectomy" and "mouse" or "rat" or "rodent", with no limitation of year of study or language. We identified a series of elements that were collected and analyzed that add up to our contemporary knowledge of this procedure. Our search returned 29 articles out of which only 15 are relevant to our purposes. Most of the current literature is concerned with the different molecular and electrophysiological issues of neuroplasticity, exhibiting the neurochemical background on which brain plasticity is founded. Experimental neurosurgery is quintessential in understanding the process in which various pathologies respond to *in vivo* animal models and recreating conditions otherwise difficult or impossible to obtain in humans. The aim of our study was to evaluate the current literature on the modern comprehension that animal models offer for histopathological, neurochemical and microsurgical research. In addition, the review is focused on the neuroplastic/compensatory mechanisms developed after hemispherectomy. Further research is of vital importance in exploring neurotherapeutical aspects of neuroplasticity in central nervous system (CNS) diseases.

INTRODUCTION

In the field of epilepsy surgery, hemispherectomy is a procedure that has undergone a long metamorphosis in time with a variation of technique and outcomes. The first indication was for a giant glioma, performed by Walter Dandy in 1928 (Dandy 1928), but the contemporary indication is in various forms of pharmacoresistant epilepsy such as cortical dysplasia, hemimegalencephaly, Rasmussen encephalitis and Sturge-Weber syndrome (Kossoff et al. 2002). The main mechanism around which hemispherectomy revolves is the brains neuroplasticity. The term refers to the brains capability to adapt to the changes that it is going through, whether it is a response to a certain pathology or a reorganization of the neural pathways that is made in order to compensate an iatrogenic event, such in the case of hemispherectomy. Brain plasticity is a real phenomenon present in adult life not only in childhood and is due to behavioral and environmental stimuli such as aerobic exercise (Mang et al. 2013) or acupuncture (Xiao et al. 2017), thought, emotions, etc. Moreover, the individual synaptic connections in adult brain are constantly removed or recreated according to the activity of the neurons or in response to training and brain injury. Practically, the central nervous system undergoes structural and functional changes in response to new stimuli (Kleim and Jones 2008), strengthens existing connections and forms new ones (Warraich and Kleim 2010) in order to improve motor skills relearning af-

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ter hemispherectomy. Our comprehension regarding the subject of neuroplasticity has grown exponentially across the years, yet the modulation of the compensation mechanism that is catalyzed in the contralateral hemispheric neurons is still a subject of debate. Regarding hemispherectomy, rodents have been intensely studied with some promising insights in this neurometabolic phenomena. The purpose of the review was to assess the current status of information provided by rodent neurohistochemistry, physiology and neurobehavioral aspects and to summarize the progress and the limitations of such an experimental model.

The rodent model constitutes a great advantage to reproduce the technique, both financially and as well as from the monitoring point of view.

A significant limitation of the rodent model in experimental neurosurgical techniques is represented by the anatomical differences of a rodent brain, as opposed to a human brain. This implies that certain interpretations and structures will not be relevant when a human subject is regarded.

METHODS

The search was conducted on the PubMed database using the search terms "hemispherectomy" and "mouse" or "rat" or "rodent" in the following search arrangement; hemispherectomy rat or hemispherectomy mouse or hemispherectomy rodent or hemispherectomy mice with no limitation of year of study or language. An evaluation was also performed on research articles that were obtained from the references cited in the papers. Inclusion criteria were reports regarding experimental aspects in rodents following hemispherectomy. Excluding criteria were constituted by the usage of primate or feline experimental models, as well as the evaluation of cerebellar hemispherectomies. The elements that have been elaborated in current literature were classified according to the investigation performed. The systematic review was assembled in conformity with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

RESULTS

Out of 29 articles, only 15 were relevant to the purpose of the study. Exclusion criteria were constituted by the data revolving solely around cerebellar hemispherectomy. The techniques and investigations performed in the cited articles were used to structure this review.

Hemispherectomy technique

The first hemispherectomy on a rodent model was researched by Hicks and D'Amato (1970) where, after craniotomy, they removed through aspiration the lateral half of the brain, rostral to the tentorium. The olfactory bulb and the optic chiasm were generally conserved. The midline was an approximate demarcation of elements from the diencephalon ventral forebrain and the neocortex (Hicks and D'Amato 1970). Table I reveals the all the techniques used in research with the various elements evaluated. Another cited technique today is the one belonging to Machado et al. (2003) and Marino et al. (2001) who, through a right craniotomy exposed the dura 3 mm anterior, 2 mm posterior to the bregma with 5 mm width and 1 mm away from the midline. Afterwards, the authors made a left craniotomy as well, along with the resection of the temporal bone and the consecutive preservation of the temporal muscle. The entire cortex with the hippocampus and basal ganglia was excised, leaving the diencephalon intact. Hemostasis was performed, the wound was closed and the recovery was allowed in a metabolic cage for 10 days (Machado et al. 2003). Krahe et al. (2001) uses a stereotaxic frame to facilitate the immobilization of the head. The process of removing the hemisphere is done mainly by aspiration with careful maneuvering of the contralateral anatomical segments. Coagulation of the middle cerebral artery was performed along with antihemorrhagic absorbable gelatin sponge. After surgery, animals were given 0.3 mg/mL subcutaneous buprenorphine analgesia (Krahe et al. 2001).

Neurodynamics of asymmetry

The motor organization projected by the absence of one hemisphere was the prime subject of investigation. The aspect of asymmetry is a matter of debate among many studies regarding the cerebral lateralization of motor functions. Paes-Branco et al. (2012) evaluated the motility performance after hemispherectomy in adult Swiss mice using the accelerating rotarod test, the foot-fault test and the elevated body swing test. They concluded that there was an unequal impairment in the motor ability dependent on which hemisphere was resected. Surgery on the right hemisphere proved to have more severe consequences compared to surgery on the left hemisphere (Paes-Branco et al. 2012). In support of the differential coping mechanism of hemispheres, immobile behavior was tested by Filgueiras et al. (2006) during a 5-min swimming test, in which an increase was observed in immobility in the right hemispherectomized Swiss mice, as compared to

Table I. An overview of hemispherectomy trials and surgical methods, as well as outcome measurement techniques.

Year	Authors	Journal	Rodent Species	Anesthesia	Technique	Investigations	Effects/Findings
1970	Hicks and D'Amato	Experimental Neurology	Neonate and Mature Wistar Rats	Ether	Under the microscope, the hemisphere was aspirated, through a burr hole	Comparative motor sensory functions, visual behavior between infant and mature animals Histology: Nauta method modified by Fink and Heimer	Absence of tactile placing contralateral to the cortical lesion, especially in infants (day 17). Discrimination of visual patterns, some of which used the opposite eye to perform the visual task. Uncrossed cortical tract (Fink-Heimer-Nauta) only in infants
1988	Gonzalo and Torramade	Developmental Brain Research	Neonate Hamsters	Hypotermia	Hemidecortication through aspiration	Histology: cresyl violet staining	Reduced number of neural elements in the extraocullar motor nuclei.
1991	Huttenlocher and Bonnier	Developmental Brain Research	Neonate Sprague Dawley Rats	Hypotermia	Removal of the cerebral cortex including hippocampus and lateral basal ganglia	Histochemistry	Differences between the density of corticospinal tracts in animal groups with amputated/ restraint limbs and with hemispherectomy
2001	Krahe et al.	International Journal of Neuroscience	Mature Swiss Mice	Tribromoethanol (i.p.)	After the removal of the parietal and frontal bones, the hemisphere, mainly the rostral part to the tentorium along with the olfactory bulb is aspirated and the remaining space is filled with gel foam	Free-swimming test Histology with cresyl violet staining	Tendency of rats to turn in the opposite direction, contralateral to the hemispherectomy
2003	Machado et al.	Epilepsia	Mature Wistar Rats	Thiopental i.p. 50 mg/kg Ketamine 100 mg/kg	After placing the electrodes in the specified regions, the hemispherectomy is performed through the unilateral removal of the whole cortex, white matter, hippocampus and basal ganglia with the preservation of the diencephalon	Electrocortical motor area mapping	The stimulation of only the right hemisphere generated bilateral body movements after 2 weeks
2006	Mameli et al.	Seizure	Mature Wistar Rats	Ether	In a stereotaxic frame, the olfactory lobes and brain hemispheres were aspirated revealing the thalamus and the quadrigeminal lamina. It was necessary to preserve the lateral diencephalic surfaces and the caudal part of the mesencephalon	Blood gas analysis Respiratory parameters EEG, ECG, Blood pressure Hypotalamic neuron activity recordings Electrotalamography Multiunit vagal nerve fibers spontaneous activity	Increase in the systemic nerve firing correlated with cardiovascular abnormalities after the induction of epileptic foci
2006	Filgueiras et al.	Behavioural Brain Research	Mature Swiss Mice	Tribromoethanol i.p.	Posterior aspects of the frontal and parietal bones were exposed and removed after a skin incision was made. By random choosing the left or right hemisphere was aspirated and the cavity was filled with Gelfoam	Swimming test, Staining with cresyl violet	After hemispherectomy, the immobility time was higher in the forced swimming test
2012	Paes-Branco et al.	Experimental Brain Research	Mature Swiss Mice	Tribromoethanol i.p.	After Machado et al. (2003) selecting which hemisphere to resect	Sensory motor interaction Histology cresyl violet staining	The performance of right hemispherectomized rats was significantly more impaired than in the left hemispherectomized animals
2015	Otte et al.	Journal of Cerebral Blood Flow and Metabolism	Mature Sprague-Dawley Rats	Fentanyl citrate 0.315 mg/mL Fluanisone 10 mg/mL Midazolam 50 mg/mL	After Machado et al. (2003)	Behavioral testing DTI fMRI Fractional anisotropy	Recovery within 2 weeks. Fractional anisotropy was maintained and white matter volume and axial diffusivity higher in the opposite cerebral peduncle. Functional adaptations in the contralateral sensorimotor network following large lesions

the opposite surgical removal (Filgueiras et al. 2006). Theories concerning the underlying explanation for this response vary from the energy sparing strategy to the maladaptive hypothesis (Bandler et al. 2000, Cryan et al. 2005a,b) in which eliminating the right cortex would deactivate the organization of stressful inputs (Sullivan and Szechtman 1995).

Another aspect investigated by Krahe et al. (2001) used the free swimming rotatory test to assess sensory asymmetry. The result consisted in a profound propensity of rotating opposite to their cortical lesion. In the swimming activity, the animals expressed a persistent intention of attaching themselves to the wall as a result of the stressful situation. According to Hicks and D'Amato (1970) there are no firm modifications in motility associated with the contralateral sensory loss in the context of hemispherectomy, thus supporting the idea that sensory asymmetry plays a role in rotatory behavior (Hicks and D'Amato 1970, Krahe et al. 2001). This was also observed in the neonatal transection of the corpus callosum (Manhães et al. 2007).

The recovery process has been studied in all articles and it exhibited an impressive capacity of improvement to the initial preoperative status with minimal damage contralateral to the lesion (Takatsuru et al. 2009). This phenomenon is primarily due to brain plasticity that occurs in the remaining hemisphere after the corpus callosum was transected. Histology in these induced experimental conditions support the idea of conservation of function. According to Zecević et al. (1989) neonatal corpus callosotomy in rodents revealed no specific histochemical alterations in the hemispheres (Zecević et al. 1989). All these aspects underline a possible independent mechanism of locomotory control for each individual hemisphere. In their experiment, Machado et al. (2003) placed a matrix of three times four electrodes on one hemisphere of seven Wistar rats and then stimulated by applying electrical current that ranged from 500-1000 mA at 10 Hz with 10 ms duration. He concluded that after two weeks, 4 rats developed a global motor capacity by stimulating the right hemisphere. The same segments on both sides had symmetric and simultaneous movements (Machado et al. 2003).

Neuroanatomical pathway reorganization

The process of recovery consists of various histological and molecular changes and the rodent brain has been a good subject for analysis. Although there may not be consistent information regarding a certain morphopathological pattern consecutive to unilateral hemispheric removal, there are some findings concerning the corticospinal tract that appears to suffer a morphological reorganization as a result of cerebral lesioning (Umeda and Funakoshi 2014, Wanakhachornkrai et al. 2014). This was observed also in Huttenlocher's study where he used limb restraint who presented a neural increase in the cortical regions in which the corticospinal neurons occurred, an aspect that was very similar with the alterations in the remaining cerebral hemisphere after neonatal hemispherectomy. This notion was explored comparative to animals with limb amputations (Huttenlocher and Bonnier 1991). Donoghue and Sanes observed that motor areas that control the vibrissae and the shoulder are augmented after forelimb amputation (Sanes et al.1992). These observations suggest that the transient corticospinal connections can supply in cases of hemispheric damage enhancing the rehabilitation system.

A reorganization of sensory and motor pathways was observed after decortication in abnormal ipsilateral projections of dorsal columnar nuclei neurons contralateral to the developed lesion. Regarding some changes in histology, Gonzalo et al. (1988) evaluated the effect on cell death in the extraocular motor nuclei in newborn hamsters. According to his findings, there was a neural decrease in these nuclei, especially in those on the contralateral side (Gonzalo and Torramadé 1988). The cerebellum also plays an important role in the pathway reorganization that provides a background for recovery. Marino et al. (2001) observed that rats that underwent contralateral hemicerebellectomy prior to cerebral hemispherectomy had a more difficult recovery in comparison to those submitted to hemicerebellectomy 2 weeks after cerebral hemispherectomy (Marino et al. 2001).

Machado's data (Machado et al. 2003) obtained after adult hemispherectomy are consistent with the findings observed after neonatal hemispherectomy (Umeda 2014, Wanakhachornkrai 2014) suggesting that neuroanatomical reorganization may occur throughout life. In addition, Otte et al. (2015) found patterns of changes in white matter integrity and functional connectivity in the contralateral brain after hemispherectomy which may be associated with the recovery of sensorimotor deficits in young adult hemispherectomized rats.

In their study, Otte et al. (2015) examined white matter in the remaining hemisphere, which proved to be significantly reduced. White matter growth in healthy rats was expected as continued fiber expansion and myelination, which is known to occur in healthy rats up to old age. Hemispherectomy had a significant role in the bilateral morphology alteration of the cerebral peduncle. Large decreases in fractional anisotropy and axial diffusivity calculated from the DTI scans suggest that, due to Wallerian degeneration, the ipsilateral cerebral peduncle has largely disappeared. Low axial diffusivity has been linked to axonal degeneration. As opposed to other studies, Otte et al. (2015) revealed that fractional anisotropy did not increase in the tissue bordering area of the hemispherectomy.

Further functional imagistic are necessary to add new details of comparison to the contemporary understanding of the mammal brain.

Neurochronological variations

The basic principle in neuronal plasticity, also known as the Hebbian principle, establishes that biochemical changes in one neuron can trigger the simultaneous activation of the neighboring synapses (Munz et al. 2014). Neuroplasticity can be defined as the final stability that results after a series of activities such as molecular, functional and structural mechanisms that co-operate into restoring the brains functions after a damaging event. Another principle (the presumed Kennard's principle) states that elderly brains adapt harder to the challenges of plasticity in comparison to younger ones. This complex process was first studied in 1970 and it refers to the brains ability to cope to the changes that occur that reduce themselves on an opposite scale to the age of the individual, therefore it is considered that the greatest period of neuroplasticity of the brain is in the early childhood. Later on, studies have suggested that this mechanism does not rely only on the age of the individual and in some cases we can see a surprising recovery in terms of neuroplasticity even in adults.

It seems that a child with left hemispherectomy can recover more from normal language compared to an adult with small focal lesions in left temporal or frontal cortex (Fitch et al. 2013). Umeda and Funakoshi (2014) suggested that in young animals, the descending pathways from the undamaged sensorimotor cortex to the ipsilateral forelimb motoneurons are reorganized after hemispherectomy in order to restore the normal motor function of the forelimb contralateral to the injury. In addition, due to suppression of input from contralateral hemisphere aberrant pathways from the motor cortex to the ipsilateral motoneurons are generated (Umeda and Funakoshi 2014).

Although it is debatable whether the works of Kennard are accurate (Kennard 1942), the effect of cell injury in the chronology of brain development remains versatile (Dennis 2010). Hicks and D'Amato (1970) found significant differences in mature and newborn rats after hemispherectomy, such as a loss of tactile placing in infants. Only after day 17, the infant rats commenced to recover. The visual tasks revealed a predominant usage of the eye contralateral to the lesion. Histologically, this is due to the supplementation with retinogeniculate fibers. Also, stride incapacitated adult rats, but was present and functional in infants. There have also been alterations at a molecular level regarding differences among neonates and adults. Cytogenetical testing was performed on hemispherectomized neonatal and adult rats in order to assess through *in situ* hybridization the presence of TNF-alpha, which is assumed to have a role as a neurotrophic factor and thus have a neurorestorative potential. The animals that underwent the surgical intervention in the first 6 to 12 days postnatal had a decrease in the TNF alpha mRNA expression in the ipsilateral neostriatum one day after surgery and then the levels increased at a significantly high value on days 7 and 30 after surgery. Maximal elevations (60% greater than opposite neostriatum) were seen in animals operated on at P6 and sacrificed 30 days post- surgery. In comparison with the neonates, the expression in the adult animals was only moderately altered, with a 20% elevation found in the ipsilateral caudate 7 days after the lesion, but no significant changes after one or 30 days survival. This could suggest that TNF-alpha can be a factor that positively influences a better recovery in postnatal brains rather than in adult ones (Kornblum et al. 1994).

Although not extensively studied, these variations in age in large resections of the brain are extremely important in evaluating a paradigm applicable in a human clinical context (Gonzalo et al. 1970).

Electroencephalographic investigations in hemispherectomy

Electrophysiological testing in living animals prove their utility in the recording the dynamics of multiple single neurons and local field potentials (LFPs). These electrical cortical aspects express and interrelated patterns of activity with behavioral elements that modulate the neural and LFP activity. Another advantage is the possibility of describing the functional connectivity through simultaneous recording from different brain regions. This can shed light on how the brain components influence one another by quantifying the synchrony between the cortical areas (Buzsáki et al. 2012). Hemispherectomy induces multiple EEG abnormalities in pediatric patients, but as shown in literature (Döring et al. 1999, Greiner et al. 2011, Smith et al. 1991) these are not an accurate predictor of their outcome. Rodent models have been subjected to this form of electrocortical investigation after hemispherectomy to observe the process that governs the interdependence of motor phenomenology and cortical control. Due to the remarkable recovery capacity of patients after the removal of a hemisphere (Machado et al. 2003) projected the theory that the hemispheres are potential separate individual cerebral motor units, an idea elaborated on their observations on mapping the murine brain before and after the neurosurgical technique. Their conclusions were that, compared to the presurgical status, the hemispherectomized animals cortical segments activated the same combination of electrodes. This is a useful result for the prospect of recovery in epilepsy patients who undergo hemispherical removal. As an extent of this aspect, Mameli et al. (2006) evaluated an epileptic rodent model on which they performed a hemispherectomy to research the context of sudden death in this pathology. Their result shows epileptic foci from the hypothalamus and mesencephalon that, when activated, correlate positively with a sudden vagal reaction that results in cardiovascular and metabolic abnormalities. The cessation of the epileptic activity lowered the parameters, so the authors concluded that in certain situations neurogenic triggers can result in spontaneous death (Mameli et al. 2006).

CONCLUSIONS

Our review investigated the current knowledge on the topic of hemispherectomy in rats. The review highlights the arguments for neuroanatomical reorganization and rehabilitation after hemispherectomy and critically analyzed the differences between recovery in young and adults rats. This information is useful in our comprehension of the phenomenon in order to open new doors for the development of rehabilitation strategies to promote neuroplasticity after large brain injuries. These techniques may enhance the potential compensatory and restorative mechanisms toward functional recovery after hemispherectomy or large unilateral cerebrovascular injury.

There are, however, gaps in the current knowledge base, which require further investigation in order to provide more documented insight into these processes.

As far as histopathology or neurochemical aspects, growth factors could be involved in compensation phenomena and have yet to be studied. Similarly, an immunohistochemistry staining for NF-kB, a factor involved in synapse transmission, or further functional MRI investigations are necessary in order to clarify the processes behind compensation in destructive or traumatic brain lesions.

Another useful concept which has yet to be put to use is a prospective study, tracking the progress of function and various measurements or investigations during the weeks after hemispherectomy.

The technique of hemispherectomy on rodents has been undergone in all cases through aspiration, but it is unclear whether other important elements from the contralateral hemisphere are not vacuumed along with the targeted cerebral tissue. The main advantage seems to be the shorter operating period, which in terms of experimental microsurgery protocol is beneficial to the outcome, as opposed to a technique in which each element is dissected, thus having a longer exposure to surgical trauma and anesthetic consequences.

Reproducing human neurophysiology in rodent models of hemispherectomy has an important role in our understanding of neuroplasticity. Various factors contribute to the phenomena of cerebral compensation and reorganization of the remaining neural tissue and to the potential of restoration of functions that can be enhanced through pharmacotherapy. Further studies must be endeavored to reveal a more accurate view on underlying processes and their applicability in clinical situations.

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