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Neuroanatomical Studies on the Tectum of Some Selected Rodent Species

***[1,2]Agbon AN, [1]Ahmad AN, [3]Mahdi O, [3,5]Bobbo KA, [3]Bala U, [4]Enemali FU, [1,2]Henry R, [1,2]Shuaib YM, and [1]Yusha'u Z**

[1]Neuroanatomy and Neurosciences Research Unit, Department of Human Anatomy, Faculty of Basic Medical Sciences, College of Medical Sciences, Ahmadu Bello University (ABU), Zaria, Nigeria.
[2]Microscopy and Stereology Research Unit, Department of Human Anatomy, ABU, Zaria.
[3]Department of Human Anatomy, College of Medical Sciences, Gombe State University, Gombe, Nigeria.
[4]Department of Anatomy, Faculty of Basic Medical Sciences, University of Medical Sciences, Ondo, Nigeria.
[5]UPM-MAKNA Cancer Research Laboratory, Institute of Bioscience, Universiti Putra Malaysia, Selangor, Malaysia.

Corresponding author: Agbon AN
E-mail: bellulu09@gmail.com; +234(0)7067434502

ABSTRACT

Comparative neurobiology provides empirical evidence to neuroscientists for the classification of biological species based on diversities or similarities of their neuroanatomical characteristics. Rodents are imperative neuroscience research tool, beneficial in elucidating brain pathologies and possible therapies where human subjects cannot be used. Tectum, a region of the midbrain, is composed of a set of colliculi responsible for initial processing of sensory information from the eyes and ears. This study comparatively assessed neuroanatomical features of the superior and inferior colliculi of some selected rodent species: Wistar rat, Guinea pig (*Cavia porcellus*) and rabbit (*Oryctolagus cuniculus*). Nine male rodents (n=3/species) were obtained for the study. Morphologic and microscopic assessments including body and brain weights, histologic and histochemical, and histometric examinations were conducted. Data obtained were compared amongst species using statistical (IBM SPSS *v*23) and imaging (AmScope, US and ImageJ, US) softwares. Results revealed remarkably ($p<0.05$) higher values for body and brain weights with rabbits, but lower for organosomatic index amongst the species. Microscopy revealed similarities, with slight variations in cytoarchitechture of the colliculi across species. Histometric characteristics of the colliculi revealed difference ($p<0.05$) in pyramidal neuronal soma size amongst the species. However, cell density in the colliculi was not different when compared. In conclusion, there exist similarities and differences in the neuroanatomic features of the tectum amongst the rodent species. These similarities are demonstrated in the morphologic and histologic features and, variations in the histometric characteristics. These findings demonstrate similar ancestry in the species and, could be beneficial in neuroscience related fields.

Keywords: Cytoarchitecture, Cell density, Histometry, Colliculi, Organosomatic index

INTRODUCTION

Comparative neurobiological assessment involves identification and elucidation of the similarities and differences in the neuroanatomical features of different organisms in relation to functions of the organisms. Comparison of structures of the nervous system amongst two or more species has aided the classification of organisms as either phylogenetically related or otherwise and long served as an established evidence for evolution.[1,2,3,4]

In mammals, the brain is the most complex structure of the body, composed of several parts and regions involved in the regulation of vital functions. A unique structure of the mammalian brain commonly visible on the ventral surface is the brainstem, composed of midbrain, pons and medulla oblongata.[5,6] The midbrain connects with different regions of the brain and, is associated with functions including vision, hearing, motor control, sleep, wakefulness, etc.[7] The midbrain is commonly described with two major regions; the tectum, dorsally and cerebral peduncles, ventrally. The tectal region presents with four rounded swellings, the colliculi (a superior and an inferior one on each sides of the brain).[7] The empirical assessment of this brain region is imperative in elucidating neurological related conditions, which requires the use of animal models.

Small laboratory animals including rodents are imperative tools for research in the fields of neurosciences, beneficial in empirical elucidation of neurological pathologies and development of possible pharmacological therapies for neurological disease conditions where primates or humans subjects cannot be used.[8,9, 10] Rodent species including rats (*rattus norvegicus*), guinea pigs (*Cavia porcellus*) and larger than guinea pig, the rabbits (*Oryctolagus cuniculus*) are commonly used animal models in biomedical research.[10,11,12] Rats are widely used in drug development and related therapies.[13] A popular strain of laboratory rats, the Wistar rat, is currently one of the most popular animal model used for neuroscience research[14,15] as effort has been made to describe the biology of the brain of this species.[16,17] Guinea pigs have been reportedly used as experimental animal model in studies related to the immune and nervous systems[18,19,20] and, rabbits reported to be beneficial in the fields of immunology, pharmaceutics and genetics.[10,21,22] Importantly, these species have biological similarities to humans, particularly in their genetic composition. Thus, beneficial in several fields of research.[23,24]

A number of studies have described the biology of these species;[25,26,27] some studies have compared the morphologic characteristics of the brain and, a few studies, certain regions of the brain.[28,29] Granted, the brain is anatomically diverse across species, presenting with structural differences, even at microscopic levels over short phylogenetic distances.[30,31,32] Consequently, there is a need to comparatively elucidate on the neuroanatomical features of the midbrain-tectum of these rodent species in order to mark out possible similarities and differences, and identify suitable species as potential models for certain neuroscience researches.

This study comparatively assessed neuroanatomical features of the superior and inferior colliculi of some selected rodent species: Wistar rat, Guinea pig (*Cavia porcellus*) and rabbit (*Oryctolagus cuniculus*).

MATERIALS AND METHODS

Experimental Animals: Healthy adult male rodent species: Wistar rats (n =3), rabbit (*Oryctolagus cuniculus*) (n=3) and guinea pig (*Cavia porcellus*) (n= 3) were obtained from the Animal House of the Faculty of Pharmaceutical Sciences, Ahmadu Bello University (ABU), Zaria, and transferred in

cages to the Neuroanatomy and Neuroscience Research Laboratory, Department of Human Anatomy, Faculty Basic Medical Sciences, ABU, Zaria. The rodents were allowed to acclimatize for few days and were euthanized thereafter.

Experimental Design: The three rodent species (Wistar rat, guinea pig and rabbits) (n= 3/ species) were weighed, euthanized under chloroform anaesthesia and skull dissected to harvest the brains from the cranial cavities for subsequent assessments (*see* Figure 1).

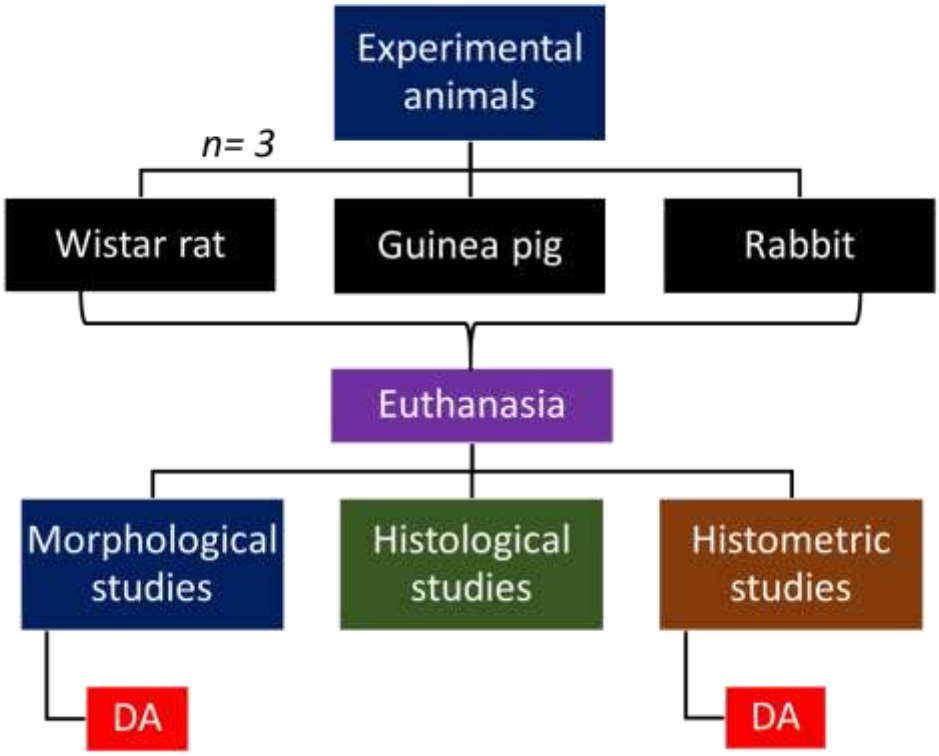

Figure 1: Experimental Design - Data analysis (DA).

Morphological Assessments: The absolute body weight of the rodents were measured using a digital scale (Electronic Kitchen Scale SF-400, China, 0.1 g,) before euthanasia; the harvested whole brains were observed for gross features, thereafter weighed using a digital weighing scale (Acculab VICON; VIC-303, USA, 0.001 g) and brain-body ratio (organosomatic index) calculated as described by Amber et al.[33]: organ (brain) weight/ absolute body weight x 100. Morphological characteristics observed were compared amongst the rodent species.

Microscopic Assessments: The harvested brain samples were fixed in Bouin's fluid for 72 hours, sectioned sagittally into two halves at the mid-line to reveal the mesencephalic (mid brain) region of the brain and subsequently processed for light microscopic examination stained with Haematoxylin and Eosin (H and E) stains to demonstrate general histoarchitectural features. Moreover, brain sections were stained with the histochemical stain, Cresyl Violet (CV), to demonstrate cytoarchitectural features and used for histometric assessments (*see* Figure 2).

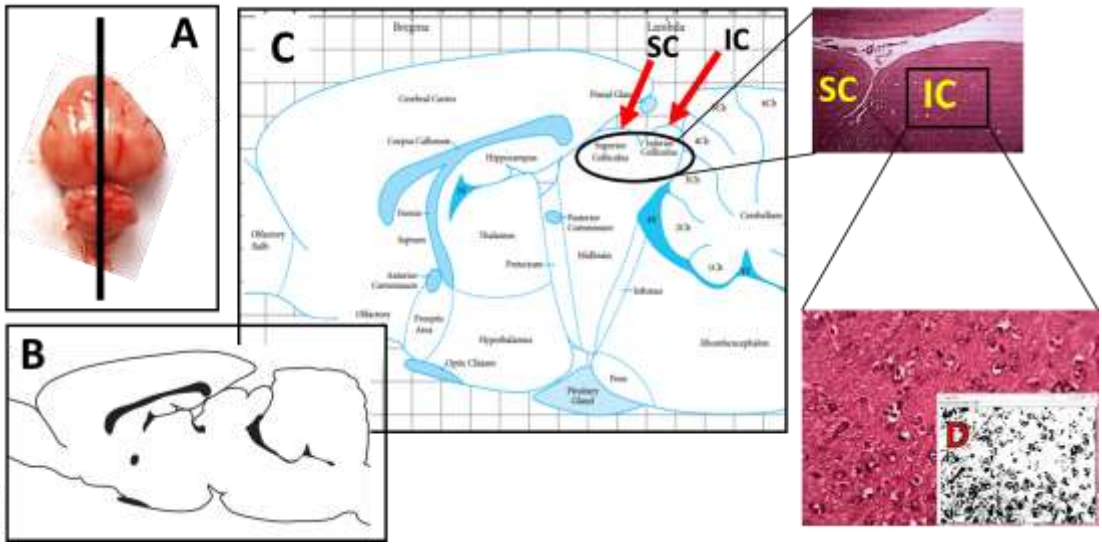

Figure 2: Brain sectioning and identification of midbrain regions - Point of sagittal section (black line) (**A**); Schematic sagittal section of the rat brain (**B**); Red arrows indicating the superior colliculus (SC) and inferior colliculus (IC) regions of the midbrain (**C**); inset, Image analysis for cell distribution (**D**). Schematic figures, B and C (Adopted from George Paxinos and Charles Watson Rat Atlas 6th edition, 2007).

Histological and Histochemical Studies: Histologically processed paraffin sections stained with H and E, and CV stains were examined for mid brain structures at the tectal region, specifically the colliculi (inferior and superior) at two magnifying powers (× 40 and 250) to demonstrate similarities and differences in the general histological and cytoarchitectural features, respectively. The Wistar rats' colliculi were identified by adopting the description in the Rat Brain Atlas,[17] which served as a reference for the identification in the two other species (*see* Figure 2). Histological tissue processing was conducted in the Histology Unit of the Department of Human Anatomy, ABU, Zaria. Light microscopic examination (using a light microscope; HM-LUX, LeitzWetzlar, Germany) and capturing of micrographs (using a Digital Microscopic Camera, MA 500 AmScope®, USA) was conducted in the Microscopy and Stereology Research Laboratory of the same facility.

Histometric Assessments: Histometric analysis was conducted as described by Agbon et al.[34] as an unbiased base for the comparison of two dimensional (2D)-quantitative cytoarchitectural features.[35] Histometric characteristic measured were the soma (perikaryon) area and soma perimeter of pyramidal neurons located in the (*inner layers of*) inferior colliculus (IC) and superior colliculus (SC) of the midbrain tectum using a light microscope with a 25/ 0.5 × objective and a micrometer slide, and a computer running imaging software (AmScope MT *version* 3.0.0.5, USA) according to the manufacturer's instruction.

Cell Density Assessments: Cell density (distribution) in IC and SC were measured from micrographs (digital microscopic images; captured at × 250 magnification) using a computer running image analysis software (ImageJ, NIH, US). The ImageJ Threshold Tool (*threshold color: Black; color space: HSB*) was employed according to the manufacturer's instruction and, the mean values for measured selected areas

were computed and statistically analyzed (*see* inset, Figure 2 D).

Data Analysis: Data obtained were analyzed using the statistical software, Statistical Package for the Social Sciences (IBM SPSS v 21.0 SPSS Inc., Chicago, USA) and results presented in charts (using Microsoft Office Excel 2013) expressed as mean ± S.E.M. The presence of significant differences among means of the groups (rodent species) were determined using one way ANOVA with *Tukey post hoc* test for significance. Paired *t*-test was used as appropriate to compare means. Confidence interval was set at $p < 0.05$.

RESULTS

Weights and Organosomatic Index: Absolute body weight assessment of the rodent species revealed significantly ($p<0.05$) higher value for rabbit compared to the other species (Figure 3 a). Similarly, comparison of the whole brain weight among the species revealed rabbit with the weightiest brain (Figure 3 b). Organosomatic index of the rodents showed remarkably ($p <0.05$) lower value for rabbit relative to Wistar rat. Guinea pig had the highest index value among the species, but not significant when compared to Wistar rat (Figure 3 c).

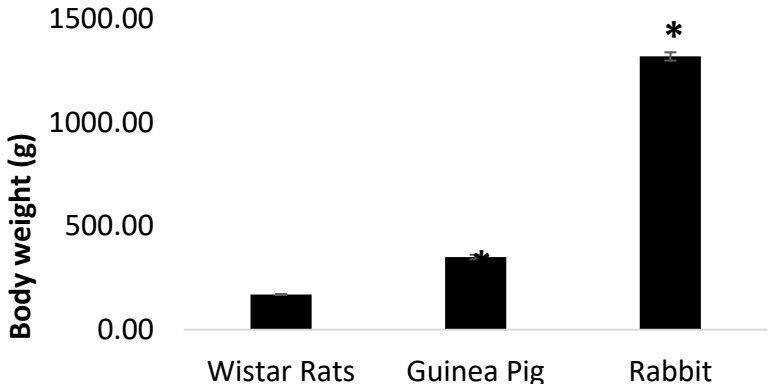

Figure 3a: Comparison of absolute body weight of rodents - n= 3; mean ± SEM; one way ANOVA *Tukey post hoc* test; *****= $p<0.01$ significant difference when compared to Wistar rat; **a**= $p<0.01$ when compared to Guinea pig.

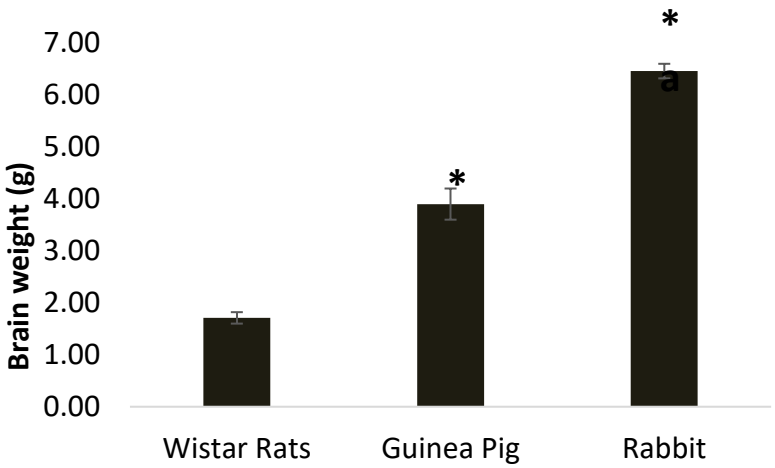

Figure 3b: Comparison of brain weight of rodents - n= 3; mean ± SEM; one way ANOVA *Tukey post hoc* test; *= $p<0.01$ significant difference when compared to Wistar rat; **a**= $p<0.01$ when compared to Guinea pig.

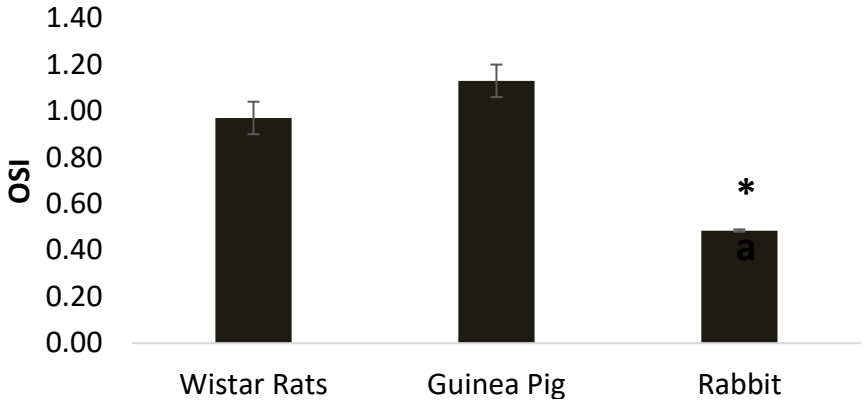

Figure 3c: Comparison of **organosomatic index of rodents -** n= 3; mean ± SEM; one-way ANOVA *Tukey post hoc* test; *****= $p<0.01$ significant difference when compared to Wistar rat; **a**= $p<0.01$ when compared to Guinea pig. OSI= organosomatic index.

Brain Gross Features: The brain of each rodent species was observed to be milky in color and, on the dorsal surface were two major depressions; a coronally oriented depression, separating the cerebrum from the cerebellum and the other, a sagittally oriented depression separating the cerebrum into two hemispheres. On the ventral surface, three distinct features; midbrain, pons and medulla which continues caudally with the spinal cord were observed (Figure 4). A sagittal section along the midline depression revealed unique features on the tectal (dorsal) region of the midbrain: two prominences (*that is*, half of the corpora quadrigemina in an intact brain) - an anterior (rostral) one, the SC and a posterior (caudal) one, the IC. The SC region was overlapped by the supero-posterior aspect of the cerebrum, while the IC region was slightly overlapped by the substance of the cerebellum (Figure 2 B and C; *see* Figure 5 A and B).

Histological and Histochemical Studies: Examination of histological and cytoarchitectural features in the sections of inferior and superior colliculi across the species revealed the following: at a lower microscopic magnifying power, across the rodent species, IC appears to have a smaller area (or mass) compared to SC. This observation however, was not quantified statistically. Posteriorly (caudally), IC is related to the lobules of the cortical cerebellum separated by a thin lining fascia (meninges). Anteriorly (rostrally), IC is related to the SC separated by a depression (sulcus) lined with fascia and white matter. The IC parenchyma revealed majorly two distinct laminae (layers); presenting the IC with an outer (superficial or cortical), narrow layer and an inner (deep or medullary), wide layer orientation. The cell distribution at the outer layer could be likened to the 'molecular layer' of the cerebral cortex manifesting with few cells and, of different types. The inner layer demonstrated with densely packed cells including neurons with prominent nuclei (Figure 5 A – C; *top row*).

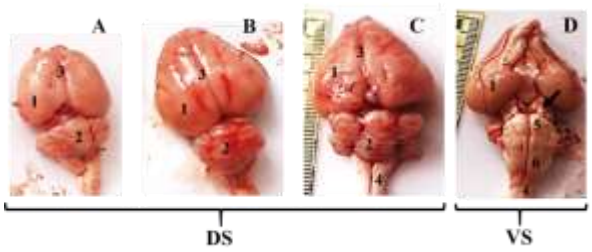

Figure 4: The brain of rodent species - Wistar rat (A), Guinea pig (B) and Rabbit (C and D); Dorsal surface (DS); Ventral surface (VS); Cerebrum (1); Cerebellum (2); Intercerebral groove (3); Spinal cord (4); Pons (5); Medulla oblongata (6)

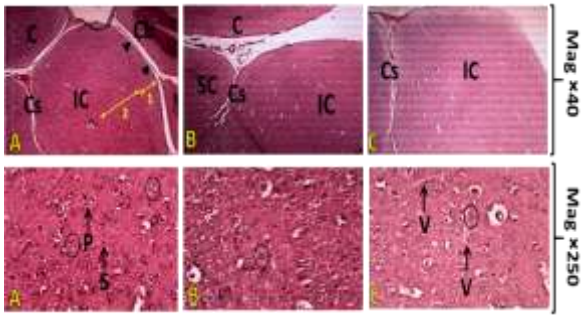

Figure 5: Micrograph of sagittal section of the midbrain (Inferior Colliculus) of Wistar rat (A), Guinea pig (B) and Rabbit (C). H &E Stain. Cerebellum (Cb); Cerebral cortex (C); Crusiform sulci (Cs); Inferior colliculus (IC); Superior colliculus (SC); Stellate cell (S); Pyramidal cell (P); Blood vessel (V) Outer layer (1); Inner layer (2); Meninges (arrow heads); Synapsing cell clusters (encircled area).

A closer observation at the inner layer of IC at a higher magnifying power revealed a variety of cells including neurons and glial cells with distinct nuclei and cytoplasm having different shapes and sizes across the species. Interestingly, some pockets of synapsing clustered cells were observed across the species, with clusters more frequent in rats. Relative to cell density, no clear distinction cloud be made from the histological sections (Figure 5 A – C; *bottom row*).

Similarly, the SC at lower magnification revealed two distinct layers; an outer and an inner one with variety of cells with different shapes and sizes. Synapsing clustered cells were observed across the species, with clusters more frequent in rats (Figure 6 A – C; *top rows*). At a closer observation, there appear to be a slight difference in the cell density amongst the species, rabbit especially (Figure 6 A – C; *bottom rows*).

Histochemically, cytoarchitectural features in the sections of the colliculi across the species revealed the following: first and foremost, the cells of the IC and SC were reactive to the CV stain. Relative to the inner layers of IC and SC, the variety of cells including neurons, interneurons and glia with different shape and sizes clearly identified were: pyramidal, stellate, horizontal, basket, fusiform (bipolar) and multipolar cells. Pyramidal and stellate cells were more frequent in rats, while horizontal cells more in guinea pigs amongst the species. Moreover, cells distribution appear to be denser in SC compared to IC across the species (Figure 7).

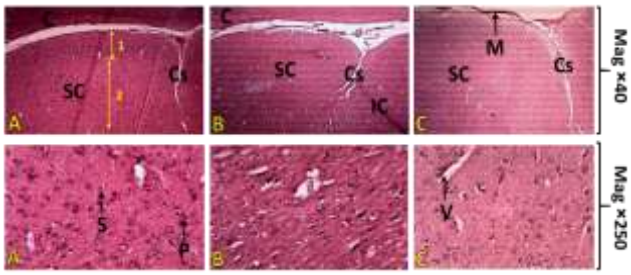

Figure 6: Micrograph of sagittal section of the midbrain (Superior Colliculus) of Wistar rat (A), Guinea pig (B) and Rabbit (C). H &E Stain. Cerebral cortex (C); Crusiform sulci (Cs); Inferior colliculus (IC); Superior colliculus (SC); Stellate cell (S); Pyramidal cell (P); Blood vessel (V) Outer layer (1); Inner layer (2); Meninges (M).

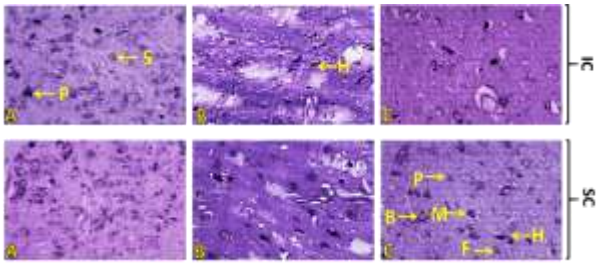

Figure 7: Micrograph of sagittal section of the midbrain of Wistar rat (A), Guinea pig (B) and Rabbit (C). CV Stain, Mag × 250. Basket cell (B); Fusiform (bipolar) cell (F); Horizontal cell (H); Inferior colliculus (IC); Superior colliculus (SC); Stellate cell (S); Pyramidal cell (P); Multipolar cell (M).

Histometric Studies: Analysis of histometric characteristics (soma area and perimeter) of pyramidal neurons of the IC revealed remarkably ($p < 0.05$) lower values with guinea pig and rabbit when compared with values for rats (Figures 8 a and 8 b). Similarly, histometric characteristics of SC pyramidal neurons showed significantly ($p < 0.05$) lower values with guinea pig relative to values for rats and rabbits. However, unlike IC, histometric values in SC were higher for rabbit compared with rats (Figures 8 c and 8 d).

Cell Distribution Analysis: Quantification of cell density (distribution) in the colliculi (IC and SC) revealed no remarkable difference when compared amongst the species (Figures 9 a and 9 b). Correspondingly, comparing cell distribution between IC and SC across the species showed no significant difference (Figure 9 c).

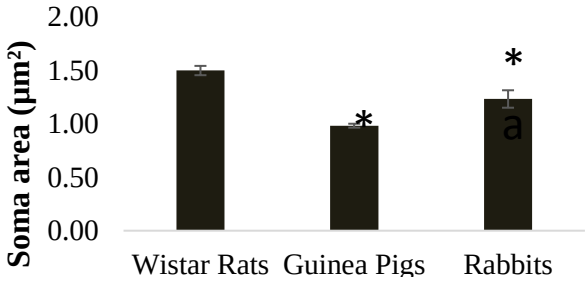

Figure 8a: Comparison of histometric characteristics (soma area) of pyramidal neuron in the inferior colliculus, Mean ± SEM; one way ANOVA *Tukey post hoc* test; *= $p<0.01$ significantdifference when compared to Wistar rat; a= $p<0.01$ when compared to Guinea pig.

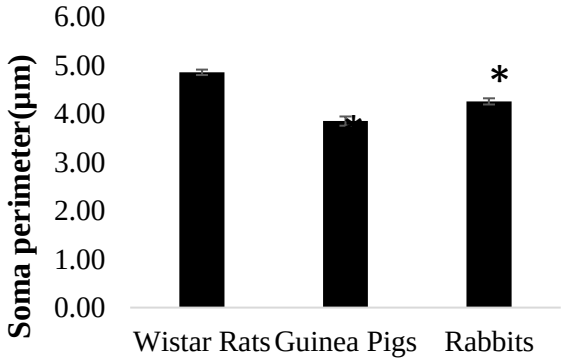

Figure 8b: Comparison of histometric characteristics (soma perimeter) of pyramidal neuron in inferior colliculus. Mean ± SEM; one way ANOVA *Tukey post hoc* test; *= $p<0.01$ significant difference when compared to Wistar rat, a= $p<0.01$ when compared to Guinea pig.

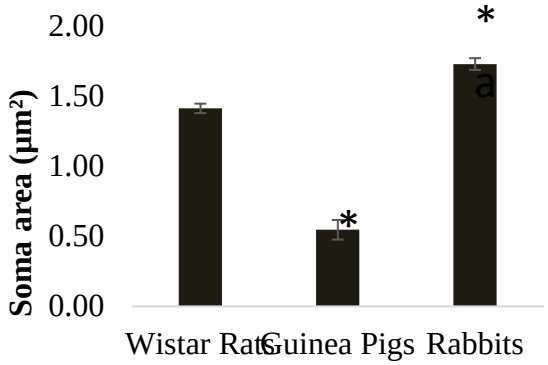

Figure 8c: Comparison of histometric characteristics (soma area) of pyramidal neuron in the superior colliculus. Mean ± SEM; one way ANOVA *Tukey post hoc* test; *= $p<0.01$ significant difference when compared to Wistar rat; a= $p<0.01$ when compared to Guinea pig.

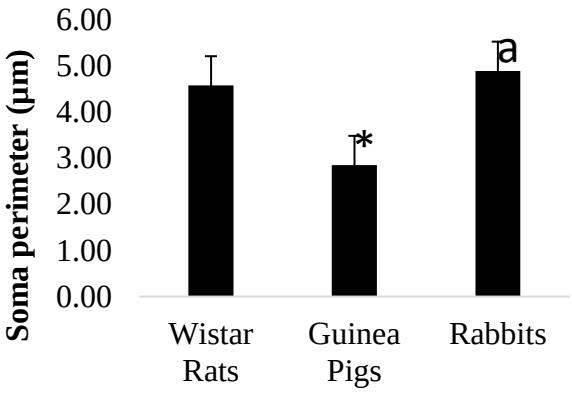

Figure 8d: Comparison of histometric characteristics (soma perimeter) of pyramidal neuron in the superior colliculus. Mean ± SEM; one way ANOVA *Tukey post hoc* test; *= $p<0.01$ significant difference when compared to Wistar rat, a= $p<0.01$ when compared to Guinea pig.

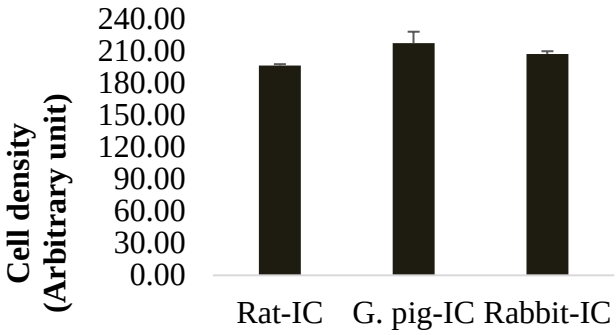

Figure 9a: Cell distribution in inferior colliculus of rodents. Mean ± SEM; one way ANOVA *Tukey post hoc test*; no significant difference when values were compared between species. Guinea pig (G. pig); Inferior colliculus (IC)

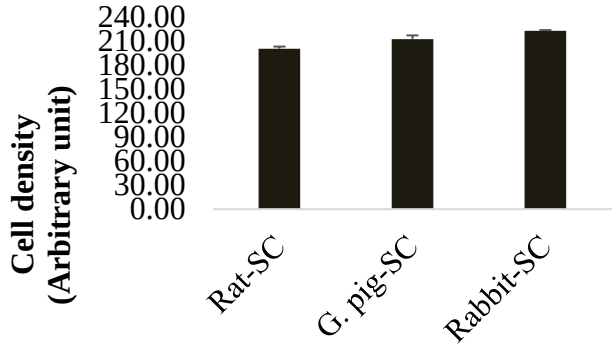

Figure 9b: Cell distribution in superior colliculus of rodents. Mean ± SEM; one way ANOVA *Tukey post hoc test*; no significant difference when values were compared between species. Guinea pig (G. pig); Superior colliculus (SC)

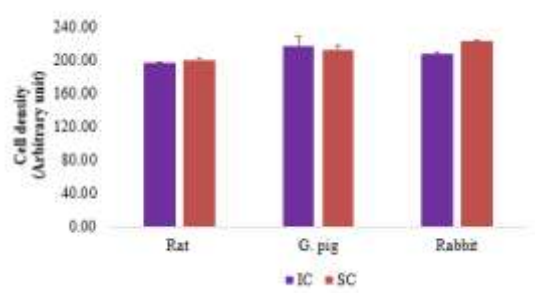

Figure 9c: Comparison of cell distribution in colliculi of rodents. Mean ± SEM; Paired *t*-test; no significant difference when values were compared between species. Inferior colliculus (IC); Superior colliculus (SC)

DISCUSSION

In this study, neuroanatomical features of the tectal-midbrain were comparatively assessed, using morphologic and microscopic approaches, among three rodent species (Wistar rat, guinea pig and rabbit).

The mean absolute body and brain weights observed to be remarkably higher in rabbits amongst the studied species could be associated to the obvious fact that rabbit has a larger body size compared to the other rodents assessed in this study. This finding is in agreement with the reported trends that associated larger body sizes (masses) to weightier animals and the bodily organs.[28,36,37] Studies have reported mean absolute body weight values for smaller rodents including murines to be lower than the mean values for larger rodents like African giant rats (*Cricetomys gambianus*; > 1 kg)[38] and greater cane rats (African grasscutter) (*Thryonomys swinderianus;* > 2 kg).[39]

Organosomatic index (brain-body weight ratio) differ from one taxon to another.[40,41] In this study, the guinea pig revealed higher values for brain-body weight ratio amongst the rodent species. This finding is in agreement with higher values for brain-body weight ratio reported in smaller rodents including mice and rats[34, 38,42] relative to lower values reported for larger species like African giant rats[38,43] and African grasscutter.[44] In mammalian species, larger relative brain weight provides for intelligence; more complex cognitive tasks, behavioral flexibility, and survival advantage.[42,45,46] Findings in this study corroborate the established benefit of Wistar rat and guinea pig as more intelligent species and suitable animal models for neuroscience researches.[47,48,49]

Brains' milky coloration observed in the species agrees with the reported appearance for rodents.[28,36] Milky to whitish coloration could be associated with high lipid components present in structures of central nervous system.[50,51] Major depressions separating the cerebrum and cerebellum and, a ventrally located brain stem with colliculi situated at the mid brain- tectum as observed in the species is in line with reported brain morphology of rodents and other mammalian species.[38,43,52,53]

Similar histoarchitectural features observed in the colliculi across the species points to convergent phylogenetic relationship, with similar mammalian ancestry.[13,54] Although not quantified, it is relevant to emphasize the observed difference in size (mass) of SC over IC. This finding is in agreement with reports of Moore and Dalley[55] in a mammalian species; superior colliculi are larger and darker than the inferior colliculi. This manifestation could be associated to the volume of structures interconnecting the SC to other brain regions including the retina, spinal cord, inferior colliculus and cortical cerebrum.[7, 56,57]

Moreover, distinct layers (laminae) demonstrated by the colliculi is in line with reports on the architecture of colliculi described with lamination.[58,59] Ito and Feldheim[60] reported that the SC in a rodent species is organized into series of laminae topographically aligned with visual field. Conversely, majorly two distinct laminae identified in this studies could be tied to the methods and techniques used for

demonstration of the microscopic features of the colliculi. Cells including nerve cells (neurons) and glial cells, and pockets of clustered cells observed across the species is typical of nervous tissue.[61,62] The presence of clustered cells is characteristic of communicating neurons and interneurons; communicating neurons involved in somato-somatic synapses, probably groups of functionally dependent cells involved in excitatory activity.[7,63]

CV is an excellent neuronal, cell body-specific stain.[64,65] Reactivity of colliculi to the histochemical dye, CV is an indication that the cells are involved in normal physiological and biochemical processes necessary for nervous tissue functionality.[64] Cytoarchitectural features of the colliculi including variety of cell types with differing shapes and sizes identified histochemically, at a closer observation on the so described 'inner layer' of the colliculi in this study is in line with the reported microscopic features of colliculi in rodents.[60] Several cell types with specific functions in the colliculi have been described in mammalian species by several workers.[66,67,68,69] Gale and Murphy[70] reported distinct four SC cell types including horizontal, stellate and multipolar cells and tagged them with certain functional properties in a rodent species. The purpose of having pyramidal and stellate cells more frequent in rats and horizontal cells more in guinea pigs amongst the species is unclear, but this manifestation may not be completely disconnected from the salient species-specific functions. This finding is line with the report of Feinberg and Meister[71] that observed heterogeneous distribution of neurons across the transverse extent of the colliculus in a rodent species. Furthermore, it is imperative to recall that one neuron could have more than one response or activity.[60,72]

Histometric quantification of 2D-histological data has been described as an imperative tool that avails the histoscientist with improved and objective basis for comparison of histological observation.[35,65] The remarkably higher values for histometric characteristics of pyramidal neurons in IC in rats is suggestive of variation in neuronal sizes amongst the species, which in turn could be a reflection of species-specific functionality. Wistar rats are generally described to be very responsive and active during night and moderately at day, thus tasking their inferior and superior colliculi more; alongside other factors including their feeding habit, lifestyle and nature of habitat.[73] Moreover, considering the critical roles of IC as the relay station for auditory pathway, optimizing the sense of hearing for rats to keep alert in a stressing environment packed with varying predators is necessary for survival.[74]

Remarkable difference in histometric characteristics of pyramidal neurons in SC in rabbit is a pointer to variation in neuronal sizes amongst the species. This finding could be associated with the size of brain, sense organ of vision and extrinsic auditory structure for the rabbit relative to the other species. Herculano-Houzel et al.[75] reported average neuronal size is larger in larger brains of mammalian species. Additionally, the SC is involved in the integration and processing of auditory and somatosensory information,[60] which could elaborate on the neuronal size for the species.

Cell distribution is critical in the homeostasis of a biological system as this reflects functionality.[71] In this study, the absence of remarkable difference in colliculi cell density amongst the species is suggestive of convergent phylogenetic relationship.

CONCLUSION

There exist similarities and differences in the neuroanatomic features of the tectum amongst the rodent species. These similarities are generally demonstrated in

the morphologic and histologic features and, variations in the histometric (cytoarchitechtural) characteristics. These findings demonstrate similar ancestry in the species and, could be beneficial in the identification of suitable models for certain neuroscience investigations that aids elucidation of related human health conditions. Despite this progress, there is still much to learn. Details on comparative assessments including stereological quantification with immunohistochemical staining for specific cell types, ultrastructure and neurobehaviour are lacking.

CONFLICT OF INTERESTS

Authors hereby declare that there is no conflict of interest regarding the publication of this article.

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