Rabies virus down-regulates gene expression of GTPases and synapse related proteins

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Background and Purpose: Rabies virus (RABV) is a neurotropic pathogen that produces severe encephalitis and terrifying neurological symptoms in humans and animals. The pathological mechanism of RABV is poorly understood, but the current studies show that the RABV preferably causes neuronal dysfunction instead of cell death or necrosis. Proteins involved in synapse and postsynaptic density are integral sub-cellular components that maintain neuronal cell shape in multiple aspects. For example, p21-activated kinases (PAKs) regulate the phosphorylation of cofilin in neuronal cytoskeleton; Rac1 is a G signaling protein belonging to Rho family of GTPases and controls orientation of cytoskeleton and growth of neuronal cell; cell division control protein 42 homolog (Cdc42) also regulates cell cycle and related signaling events.

Methodology: Western blotting, immunohistochemistry and real time PCR were carried out to determine the interaction of street and fixed strains of RABV with associated mediators and binding partners of cofilin mediated pathway.

Results and Discussion: RABV inhibits the gene expression of PAK, phosphorylated cofilin and total cofilin that ultimately interferes with interacting partners such as Cdc42 and Rac1. These changes perhaps cause depolymerization of filamentous actin in neuronal cytoskeleton of hippocampus. Moreover, the street RABV infection also hampers the binding of GTP Rac1 and Cdc42 with PAKs. Street RABV also causes significant reduction in the content of active Rac1 (GTP binding form), while total Rac1 contents remain unchanged after 1 hour of infection. It can also inhibit the transformation of inactive Rac1 to active Rac1 without affecting the expression of total Rac1.

Conclusions: RABV may alter the structural and physiological architecture of dendritic spine as well as postsynaptic density by reducing the amounts of specific proteins involved in maintaining the shape of dendritic spines.

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Fluorescent Isothiocyanate Dextran evaluates the permeability of blood-brain barrier in rabies infected brain of mice

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Background: Acute encephalitis develops as the rabies virus (RABV) enters to the central nervous system by crossing the blood brain barrier (BBB) which is a tight junction of endothelial cells. In this study, three different molecular weight (70 kDa, 150 kDa and 200 kDa) of fluorescent isothiocyanate dextrans (FITC-Dextrans) were used to measure the extent of BBB damage and subsequent leakage patterns in brain tissues of rabies infected mice which were post-immunized with neutralizing antibodies to observe whether it has positive effect on infected mice by decreasing the death ratio.

Methods: The brains were processed for immunofluorescence to observe the neutralizing antibodies and its relevant compatibility with the leakage of FITC-Dextrans.

Results: Results showed that 70 kDa and 150 kDa FITC-Dextrans efficiently crossed BBB, and produced fluorescent illumination mainly in the cerebral cortex of brain. The enhancement of BBB permeability was significant at 5th day of post-immunization, while the neutralizing antibody neutralized some particles of RABV by crossing BBB, but it did not present enough treatment effect to the dying mice.

Conclusions: Taken together, these findings suggest that FITC-Dextran is an important fluorescent marker to investigate the integrity of BBB permeability in severe neurodegenerative diseases like rabies.

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Burden of dog-bites and associated risk of rabies in public sector hospitals of Punjab, Pakistan

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Rabies is an underestimated, lingering and neglected tropical disease in Pakistan. The present study was designed to investigate the burden of bite cases in humans, associated disability adjusted life year score (DALYs) and risk of rabies. The data were obtained from 4 district headquarter hospitals (DHQs) of Punjab, Pakistan which are maintained by the government and considered as an easy access health facility for the public.

Methods: The data were manually procured from the outdoor patient department from 2 hospitals during 2006 to 2012, while similar method was carried out to obtain the data from remaining 2 hospitals during 2012 to 2017. It was manually categorised into number of total bites to male, female and children with specie causing the bite. Analysis of variance was carried out to statistically analyse the data obtained.

Results: The highest cases (n = 310) were recorded in 2017 carrying the maximum number of male patients in one DHQ. The monthly distribution of bites were higher in summer with highest figure (>80%) of DALYs caused by category II bites, while limited number (>10%) of DLAYs was reported due to category III bites. The case of dog bite with essential requisites from a single patient was neither uniformly composed in hard form nor it was stored in soft form for future surveillance or national control plan.

Conclusions: Rabies is still endemic in Pakistan due to various epidemiological constraints including inadequate and insufficient prophylactic measures in basic health units of Pakistan, increasing population of unvaccinated stray dogs, lack of responsible pet ownership. Most importantly, lack of proper diagnostics and higher economic cost towards the prevention and elimination of rabies are the barriers behind legislative negligence. Moreover, lack of public awareness, and poor perceptions of health practitioners towards rabies are also causing higher number of dog bites in population.

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