

20th CENTURY EXPERIMENTAL STUDIES ON RABIES IN ANIMALS**C K SINGH^{a1}, K. BANSAL^b, M DANDALE^c, AND PRANOTI SHARMA^d**

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The present review presents the compilation of experimental studies on rabies using various virus strains on various animals. The virus propagation methodology and titration of virus isolates have been discussed as reported by various workers. Dose and routes of inocula used by various workers have also been discussed.

KEYWORDS : Dose, Experiment, Rabies, Route, Virus

Experimental studies are highly significant for understanding the processes and complexities of the disease as it provides the researcher with controlled values and environment. However, with era of stringent regulations of Institutional Animal Ethics Committee (IAEC) at the institutional as well as national levels, the experimental studies regarding research work in universities and other academic institutions have significantly decreased if not halted altogether. As such, it is pertinent to preserve the experimental findings of the yester century for the reference of present day researcher that largely depends upon the archived samples or naturally prevalent clinical cases as convenient research models.

The present review envisages the activities associated with experimental studies on rabies in animals. It incorporates isolation, titration and propagation of rabies virus. The review covers the information on virus strains used in experimental studies along with the routes and dosage of rabies virus by which various animal species were infected under experimental conditions.

ISOLATION OF RABIES VIRUS

Different workers have isolated street rabies virus from different animal sources viz. dogs (Aghomo et al., 1990; Jayakumar et al., 1990 and Madhusudana & Aggarwal 1991); fox (Baltazar et al., 1986; Sodja, 1986a; Blancou et al., 1987; Gribencha et al., 1989; Gribencha, et al., 1989a; Blancou et al., 1991 and Silva et al., 1992); mongoose (Madhusudana and Tripathi, 1990); bat (Trimarchi et al., 1986; Soria Baltazar et al., 1988; Botvinkin et al., 1988 ; Romero et al., 1991) and Silva et al.,

1992) skunk (Hill & Beran, 1992) cow (Torres Anjel et al., 1986 and Torres Anjel et al., 1988) and buffalo (Madhusudana & Tripathi, 1990 and Madhusudana and Aggarwal, 1991).

Botvinkin et al., (1987) as also Delprieto and Konolasaisen, (1991) have used the technique of mice inoculation by intracerebral route for isolation of rabies virus from bat (*Vespertilis murinys*). Stohr et al., (1992a) has reported to have isolated 1046 isolates of rabies virus from 17 animal species by employing two monoclonal antibodies. In a study on use of tissue culture technique for isolation of rabies virus, it was found that without cell adaptation it was not always possible to detect rabies antigen brain tissues infected with street strains because of the very low concentration of virus (Tollis et al., 1988), however, tissue culture technique has been employed for isolation of rabies virus from 115 to 119 animal brains in Ethiopia (Mebatsion et al., 1989).

PROPAGATION OF RABIES VIRUS

New born mouse (less than 7 days old) had been declared as the most susceptible host known for the propagation of rabies virus by Casals, (1940). Later, Kaplan, (1973) also stated that the suckling mouse is the most susceptible animal for the inoculation test.

The route of inoculation for propagation of rabies virus has also been recommended by Casals, (1940) when he recorded that the intra-cerebral route of inoculation was 10 to 100 fold or more sensitive than peripheral routes depending on virus titer. Bishop, (1979) has reported that adaptation of several rhabdoviruses to cell culture had been found to be difficult or impossible.

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TITRATION OF RABIES VIRUS

Adaptation of fixed strains of rabies to mice lead to production of titers upto 106 MLD₅₀ /0.03 ml of brain suspension. Titers of unadopted street virus are commonly lower by a factor of upto 1000 fold (Mason, 1942). Wiktor and Clark, (1973) have recorded that the most practical & precise assay of rabies virus is obtained by plaque assay - a technique only applicable to cell culture adapted fixed strains of rabies virus.

EXPERIMENTAL STUDIES

Successful transmission of rabies virus to experimental animals dates back to 1879 (Galtier, 1879).

Virus Strain

Although some workers have conducted experimental work with challenge virus strain (CVS) of fixed rabies virus (Lafon et al., 1988; Jackson and Reimer, 1989; Kosanovic and Knezevic, 1990; Madhusudana and Tripathi, 1990; Movsesiants et al., 1991; Dutta, et al., 1992 a; Silva, et al., 1992; and Smart & Charlton, 1992) or with variants of CVS strain viz. RV 194-2 (Jackson, 1991) or AvO1 (Yang & Jackson, 1992), however, most of the experimental studies reported have employed street rabies virus (Sharpee et al., 1985; Baltazar et al., 1986; Matouch & Dousek, 1986; Trimarchi et al., 1986; Blancou et al., 1987; Charlton et al., 1987; Dietzschold et al., 1987; Hati & Sarkar, 1987; Bundza & Charlton, 1988; Fekadu, 1988; Rajan & Padmanaban, 1988; Soria Baltazar et al., 1988; Torres Anjel et al., 1988; Ganiere et al., 1989; Gribencha et al., 1989; Gribencha et al., 1989a; Hanlon et al., 1989; Lodmell et al., 1989; Aghomo et al., 1990; Jayakumar et al., 1990; Blancou et al., 1991; Madhusudana & Aggarwal, 1991; Romero et al., 1991; Hill & Beran, 1992; Smart & Charlton, 1992 and Balachandran & Charlton, 1994).

One of the early studies in this regard has recorded that fixed strains show greatly diminished capacity for inducing infection by peripheral routes (Lepine, 1938).

Animal Species

Different workers have conducted experimental studies on rabies in different species of animals viz. dog (Fekadu, 1988; Fekadu, et al., 1988; Jayakumar et al., 1990; Sharpee et al., 1985; Kosanovic & Knezevic, 1990; Jayakumar & Ramadass, 1991; Blancou et al., 1987; Aghomo et al., 1990; Gribencha et al., 1989; Gribencha et

al., 1989 a; Ganiere et al., 1989); cat (Fekadu et al., 1988; Blancou et al., 1987; Ganiere et al., 1989; Trimarchi et al., 1986; Sharpee et al., 1985); sheep (Baltazar et al., 1986; Blancou et al., 1987; Soria Baltazar et al., 1988; Blancou et al., 1991; Demetradze & Sefaroz, 1991) and cattle (Torres Anjel et al., 1986; Demetradze & Sefaroz, 1991). The experimental studies conducted on wild animal species include those in skunk (Charlton et al., 1987); ferret (Matouch & Dousek, 1986; Jonsson et al., 1988); fox (Soria Baltazar et al., 1988; Kieny et al., 1988; Brochier et al., 1989; Hanlon et al., 1989); raccoon (Hanlon et al., 1989; Artois et al., 1989; Blancou et al., 1991; Smart & Charlton, 1992; Hill & Beran, 1992; and Balachandran & Charlton, 1994). Various workers have also conducted the experimental study on different laboratory animals viz. mice (Hati & Sarkar 1987; Fekadu et al., 1988; Jackson & Reimer, 1989; Movsesiants et al., 1991; Yang & Jackson, 1992; Jackson, 1991; Shankar et al., 1991; Dutta et al., 1992; Madhusudana & Tripathi, 1990; Silva et al., 1992; Blancou & Sitte, 1988; Lafon et al., 1988); rat (Gillet et al., 1986 and Torres Anjel et al., 1988); guinea pig & hamster (Madhusudana & Tripathi, 1990).

Route of Inoculation

Various routes of inoculation have been used by different research workers to conduct experimental study of rabies in different species e.g. intra-cerebral in dogs (Fekadu et al., 1988; Kosanovic & Knezevic, 1990; Gribencha et al., 1989; Gribencha et al., 1989a; in cats (Fekadu et al., 1988); stereotoxic inoculation into specific nuclei (Gillet et al., 1986); intra-muscular in dog (Blancou et al., 1987); sheep (Baltazar et al., 1986 and Blancou et al., 1987); fox (Soria Baltazar et al., 1987); raccoon (Artois et al., 1989 and Hill & Beran, 1992) ferret (Matouch & Dousek, 1986); cat (Trimarchi et al., 1986; Blancou et al., 1987); cattle (Demetradze & Sefaroz, 1991; Romero et al., 1991); Oral in mice, guinea pig and hamster (Madhusudana & Tripathi, 1990) and in South African Kudu an herbivore (Sullivan, 1985) intra-peritoneal in mice (Lodmell et al., 1989); intra-nasal in rat (Gostonyi et al., 1991) and mice (Lafay et al., 1991).

In addition to the single route of inoculation, various workers have studied the combination of different

routes of inoculation during their experimental study of rabies.

Dissemination of rabies street virus was studied in 30 mice experimentally infected by different routes. 12.5% of mice were rabies positive in pre-clinical stage. In addition to brain, involvement of salivary glands, facial skin and cornea was observed in 66.3, 72.2 and 33.3% mice respectively by intra-cerebral infection. The first appearance of the virus in the brain was observed on 3rd day in spinal cord and salivary gland on 4th day (Hati and Sarkar, 1987).

Localization and distribution of fixed rabies virus antigen was studied in experimentally infected mice by different routes. Following intra-cerebral routes, the virus was established in cortical and sub-cortical neurons and ammon's horn whereas s/c inoculation was characterized by fluorescent staining in cerebral trunk, cerebellum and to a lesser extent in sub-cortical layer (Movsesiants et al., 1991).

Difference in development of clinical signs by inoculation of CVS strain of fixed rabies virus in mice was studied. No marked variation in classical signs due to variation of routes of inoculation could be detected (Dutta et al., 1992).

Difference in the neuro-virulence of AVO1 strains with different routes of inoculation was studied (Yang and Jackson, 1992) AVO1 strain of rabies virus was avirulent by intra-cerebral and peripheral route inoculation but was neurovirulent with stereotaxic brain inoculation in either of the striatum of cerebellum of adult mice (Yang and Jackson, 1992).

A combination of intra-cerebral, footpad & oral (Fekadu et al., 1988); intra-cerebral & intra-planter in mice (Hati & Sarkar, 1987); footpad & intra-cerebral in mice (Jackson & Reimer, 1989); intra-muscular and intra-nasal in skunk (Smart & Charlton, 1992); intra-cerebral and intra-striatal in mice (Yang & Jackson, 1992); intra-cerebral, intra-venous, intra-muscular and intra-ocular (Dutta et al., 1992); intra-cisternal and intra-masseter in dog (Jayakumar et al., 1990); intra-muscular, subcutaneous and intra-cerebral in mice (Sodja, 1986); intra-spinal cord and intra-tongue in calves (Torres Anjel et al., 1986) and intra-muscular and intra-ocular in puppies (Aghomo et al., 1990).

Dose of Inoculation

Different research workers have inoculated varied doses of rabies virus in their experimental studies viz. 105.76 MICLD₅₀ by Baltazar et al. (1986); 105 MICLD₅₀ by Matouch & Dousek (1986); 3 Million MICLD₅₀ 0.03 /ml by Gribencha et al. (1989a); 106 MICLD₅₀ by Hanlon et al. (1989); 103.89 MICLD₅₀/0.03 ml by Jayakumar et al. (1990); 106.5 and 107.5 MICLD₅₀ per 0.03 ml by Madhusudana & Tripathi (1990); 5 x 10⁶ LD₅₀ by Demetradze & Safaroz (1991) 50x10⁶ LD₅₀ by Romero et al. (1991) and 1000 MICLD₅₀/0.03 ml by Dutta et al. (1992). In addition, Certain workers have also tried graded doses of inoculation to study the effect of varying doses of inoculation. Such studies have been conducted by Charlton et al., (1987); Soria Baltazar et al., (1988); Gribencha et al., (1989); Artois et al., (1989) and Hill & Beran (1992).

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