Septal Projections to Nuclei Functioning in Oxytocin Release [1]

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ABSTRACT Terminal degeneration was observed in the paraventricular and supraoptic nuclei of the hypothalamus following lesions in the septum of the squirrel monkey. The degeneration was usually greater in the supraoptic nucleus. A lesion in the posterior dorsal septum resulted in more degeneration in the paraventricular nucleus. Lesions in the dorsal gyrus rectus, genu of the corpus callosum and extreme rostral septum resulted in no identifiable degeneration in the two nuclei. These nuclei have been shown by various investigators to facilitate milk ejection (oxytocin release). Stimulation of the mesencephalic central gray has been shown to influence oxytocin release. Following a lesion in the mid-septal area, degenerating terminals were seen in the mesencephalic central gray. Our results show that the septum is directly connected with the supraoptic and paraventricular nuclei and mesencephalic tectum. Possibly the septum functions in modulating mechanisms having to do not only with lower autonomic responses such as blood pressure, and bladder emptying, but oxytocin release as well.

Stimulation of the mammary gland by suckling or manual manipulation produces impulses which effect oxytocin release. The supraoptic and paraventricular hypothalamic nuclei have been shown to affect oxytocin release (Olivecrona, '57; Nibbelink, '61). As impulses from the mammary gland ascend the neural path, they are analysed and modulated at several levels before reaching the paraventricular and supraoptic nuclei. The brain stem reticular formation plays a role of analysis and integration of the first order (Nauta, '63). It receives a massive influx of fibers from the lemniscal systems conveying general extroceptive, proprioceptive, and viscероceptive sensory modalities. Consequently, signals from the midbrain reticular formation could be transmitted to the supraoptic and paraventricular nuclei by way of rostral projections, such as, mamillary peduncle (Cowan, Guillery and Powell, '64), rostral mesencephalic gray matter, and particularly the dorsal longitudinal fasciculus (Morest, '61; Nauta and Kuypers, '58). Stimulation of numerous cerebral areas results in the release of oxytocin (Denamur, '65). Furthermore, a great variety of sensory and emotional stimuli are known to affect its release (Newton, '61; Cross, '61b). Therefore, other areas are also involved in systems of analysis and integration of oxytocin mechanisms. Stimulation of the mammary gland evokes distinct activation patterns in the hypothalamus, septum, hippocampus, thalamus and cortex (Holland and Cross, '61). This stimulation facilitates the rate of firing of some neurons in the preoptic area and midline thalamic nuclei (Cross and Green, '59). Electrical stimulation of the medial and lateral preoptic areas, septum, dorsal hippocampus, fimbria of fornix and cingulate gyrus results in liberation of oxytocin (Beyer, Anguiano and Mena, '61; Cross, '61a, b; Cross and Silver, '61; Schimizu and Kurotsu, '56). Hence, there is evidence that the limbic system may play a prominent role in oxytocin release. Terminal degeneration was observed in the supraoptic and paraventricular nuclei following lesions in the preoptic region in cats (Nauta, '58). He concluded that these nuclei appear to receive some direct connections from cell groups intercalated in the limbic system-midbrain circuit. The present study pre-

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sents evidence that the septum is also didectly connected with the supraoptic and paraventricular nuclei.

METHODS

The data for this study were obtained from four cases selected from an analysis of ten squirrel monkeys weighing 400 gm or more. The animals were anesthetized with an intraperitoneal injection of 0.2 ml (5 mg/ml) of phencyclidine (Sernylan^{R}) per kg of body weight. Xylocaine (0.5%) was used locally where needed. Each monkey was oriented in a Labtronics stereotaxic instrument for the accurate positioning of a monopolar stainless steel electrode. It was 350 μ in diameter and insulated with Epoxylite except at its tip. The electrode was placed in the septum by inserting it through a small trephine opening made in the skull by means of a dental drill fitted with a small burr. Stereotaxic coordinates ranged between A-11 and A-13, from L ¼ to L ½, and H + 7 to H + 5. After the electrode was positioned, the cathode lead of a direct current source was attached to the scalp and the anode lead was attached to the upper free end of the electrode. Small lesions were obtained by passing one milliampere of current through the septal focus for ten seconds. Twenty days post-operatively the animals were anesthetized (Nembutal^{R} 0.5 ml of a 50 mg% solution) and perfused with one liter of normal saline containing 0.5 gm of sodium nitrite. The perfusion was continued using

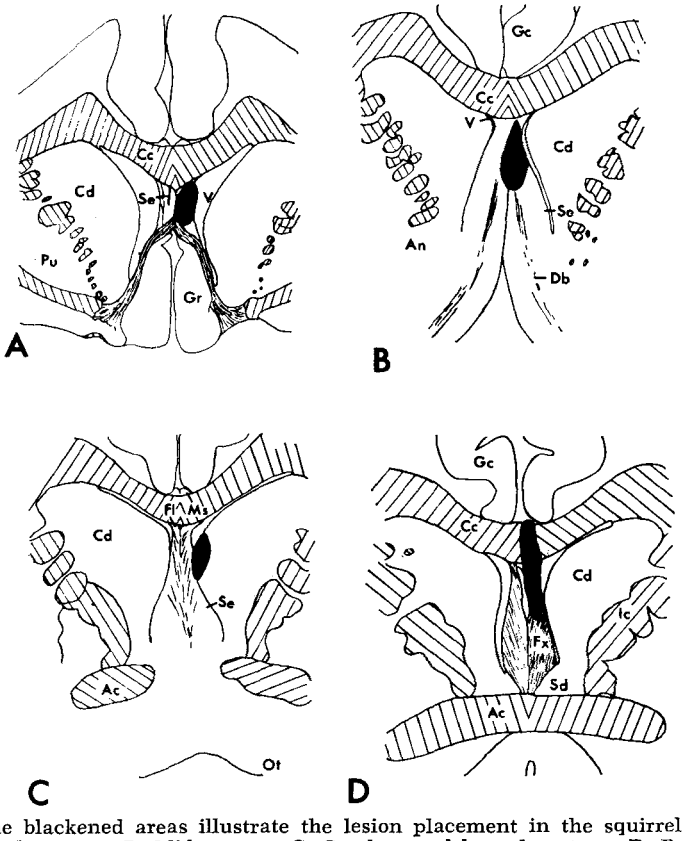

Fig. 1 The blackened areas illustrate the lesion placement in the squirrel monkey septum. A, Rostral septum; B, Mid-septum; C, Caudate and lateral septum; D, Posterior dorsal septum. Abbreviations: Ac, anterior commissure; An, nucleus accumbens; Cc, corpus callosum; Cd, caudate nucleus; Db, diagonal band; Fl, fornix longus; Fx, fornix; Gc, gyrus cinguli; Gr, gyrus rectus; Ic, internal capsule; Ms, medial longitudinal stria; Ot, olfactory tubercle; Pu, putamen; Sd, bed nucleus of the stria terminalis; Se, septum; V, lateral ventricle.

one liter of 10% formalin in normal saline. The head, with six square centimeters of calvaria removed, was separated from the body and stored in 10% formalin in the refrigerator. The following day the brain was removed from the skull, placed in fresh 10% formalin, and returned to cold storage. Three weeks later serial frozen sections were made and stained (Nauta and Gygax, '54) to demonstrate degenerating axons and their preterminals (terminals). Other sections selected from the series were stained with cresyl violet to assist in the identification of cerebral nuclei.

RESULTS

Following lesions in the septum of the squirrel monkey, degenerating terminals were observed in the paraventricular and supraoptic nuclei of the hypothalamus. A lesion involving the caudate nucleus and

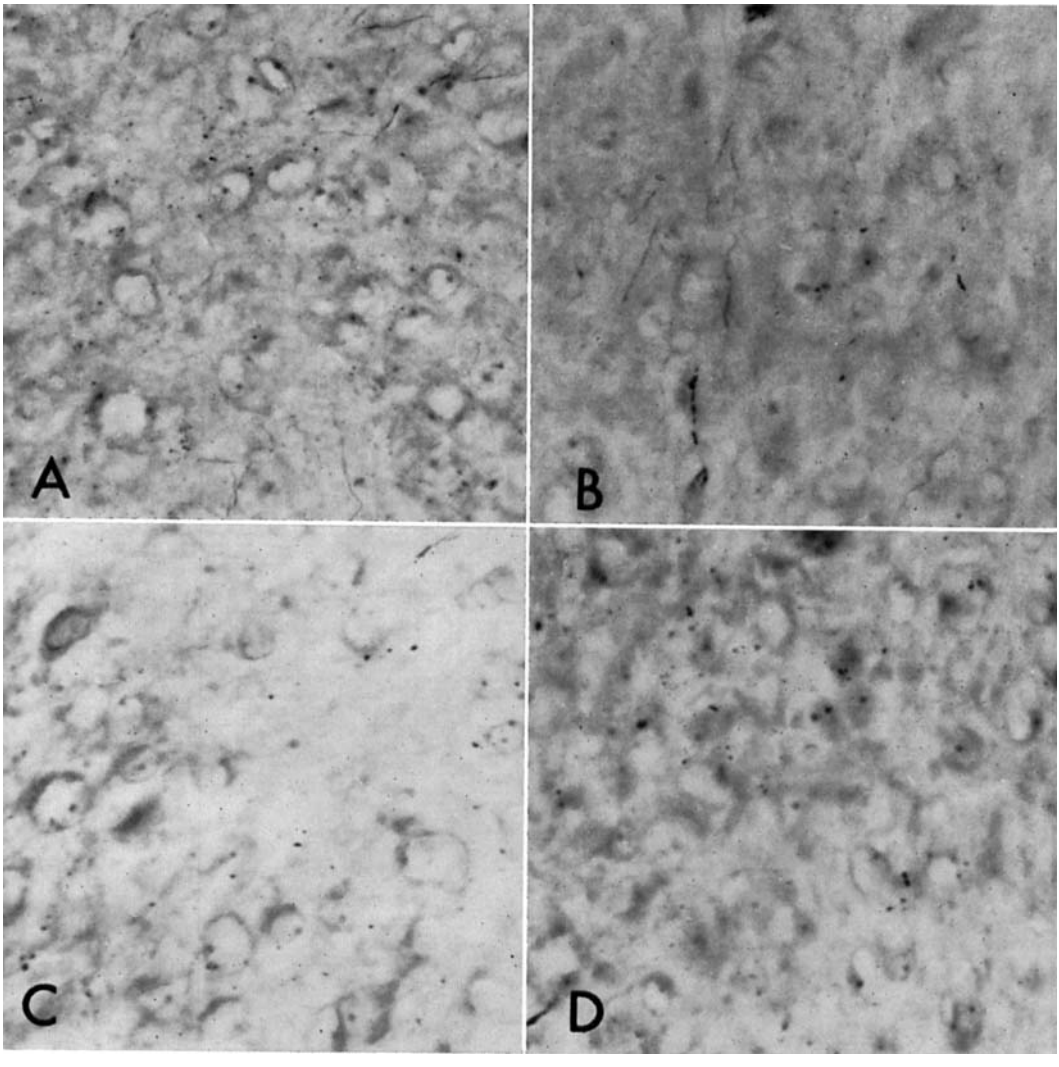

Fig. 2 Photographs show terminal degeneration. A, Supraoptic nucleus following lesion in caudate and lateral septum; B, Paraventricularis nucleus following lesion in caudate and lateral septum; C, Supraoptic nucleus following lesion in posterior dorsal septum; D, Paraventricularis nucleus following lesion in posterior dorsal septum.

lateral septum (fig. 1C) resulted in more extensive terminal degeneration in the supraoptic nucleus than in the paraventricular nucleus (fig. 2A,B). Degeneration was slightly more dense in the supraoptic nucleus in all cases except one. In this case, the lesion was located in the posterior dorsal septum (fig. 1D) and resulted in terminal degeneration slightly more heavy in the paraventricular nucleus than in the supraoptic nucleus (fig. 2D,C). Most marked terminal degeneration observed in either nucleus followed a midseptal lesion involving the medial septal nucleus and diagonal band (fig. 1B). Degenerating terminals were more dense in the supraoptic nucleus than in the paraventricular nucleus. Furthermore, they were distributed more heavily to the lateral part of the supraoptic nucleus.

The midbrain central gray also contained diffuse terminal degeneration in its dorsal and ventral part. Degenerating terminals were observed in the nucleus centromedi-

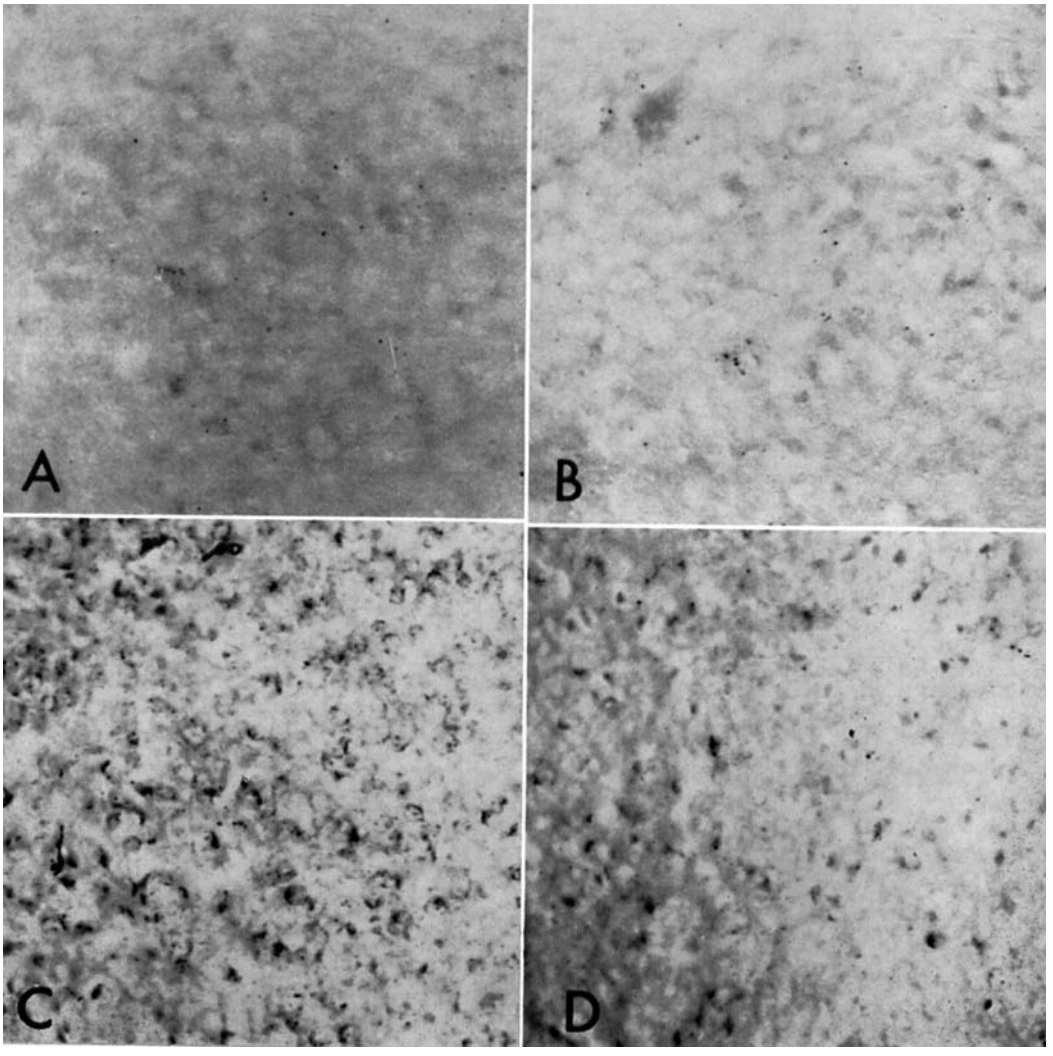

Fig. 3 Photographs show terminal degeneration following midseptal lesion. A, Dorsal central gray; B, Ventral central gray; C, Nucleus centromedianum; D, Nucleus reuniens.

anum and nucleus reuniens in all cases (fig. 3). Of the structures considered in this paper, terminal degeneration was heaviest in the nucleus centromedianum. However, the heavy degeneration to principal target structures such as the mammillary body, hippocampus and anterior thalamic nuclei are not considered in this study.

In three other animals, lesions were placed more rostrally in the most rostral apex of the septum (fig. 1A), in the dorsal gyrus rectus, and in the genu of the corpus callosum. Degenerating terminals were not seen in either the paraventricular or supraoptic nuclei in any one of these.

DISCUSSION

The results show that the septum projects directly to the supraoptic and paraventricular nuclei. Furthermore, direct connections were also shown to exist with the mesencephalic central gray, midline thalamic nuclei, and centromedian intralaminar nucleus. These structures have been shown to influence oxytocin release, except for the centromedian intralaminar nucleus (Cross and Silver, '61; Schimizu and Kurotsu, '56).

The septum is directly connected to the isocortex. The principal connections are made with the gyrus cinguli, orbital frontal cortex, suprasylvian and ectosylvian gyri, (McLardy, '55; Powell, '64; Powell, '66; Pribram, Lennox and Dunsmore, '50). The first two cortical areas have been shown to influence oxytocin release (Beyer, Anguiano and Mena, '61; Cross, '61b). Thus, the septum, a limbic structure having to do with neuroendocrine mechanisms, is structurally connected with the overlying cerebral cortex and lower autonomic nuclei.

Perhaps much of the function ascribed to the septum manifests itself through modulatory mechanisms pertaining to oxytocin release and serves as an 'on-off relay' to the paraventricular and supraoptic nuclei. Stimulation of the septum facilitates oxytocin release (Cross and Silver, '61). Our results show that the fiber projection from the midseptal area is chiefly to the supraoptic nucleus and mainly to the paraventricular nucleus following a lesion placed in the posterior part of the septum. Since this anatomical differential exists in the septum, it would seem that some areas of this structure might inhibit milk ejection, although no references were encountered which report such a result. Many of the fibers in the dorsal part of the posterior septum are fornix fibers, and as such involve interconnections of the hippocampus. From our results these could be fibers of the hippocampus projecting to the paraventricular nucleus which in turn influences oxytocin release. However, no reference was found where stimulation of the hippocampus inhibited milk ejection. The absence of evidence pertaining to an inhibitory role may indicate that such functions occur at a different cerebral level or pertain to special diffuse inhibitory mechanisms.

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