and diptera[6] is well established; similarly, ongoing attempts to characterize chemically such materials from the tobacco horn worm *Manduca* currently indicate substantial chemical similarity between the active substances from these species and the glucagon of vertebrates with intra-specific biologic activity[12]. We therefore believe that a family of peptide hormones, closely resembling the hyperglycemic hormones of crab and scorpion, may be generally operative as hormones in many insects. It will thus be of considerable interest to characterize such molecules from a great variety of arthropods, and to examine the effects of currently available materials in additional species.

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2 J.E. Steele, Nature *192*, 680 (1961).
3 G.J. Godsworthy, J. Insect. Physiol. *15*, 2131 (1969).
4 J. Dutrieu and L. Gourdoux, C.r. Acad. Sci. Paris *265*, 1067 (1967).
5 G.M. Natalizi and N. Frontali, J. Insect. Physiol. *12*, 1279 (1966).
6 S. Friedman, J. Insect. Physiol. *13*, 397 (1967).
7 P. Sreenivasula Reddy and R. Ramamurthi, Toxic. Lett., in press (1981).
8 P. Sreenivasula Reddy and R. Ramamurthi, Indian J. exp. Biol. *19*, 472 (1981).
9 D. Venkataramanaiah and R. Ramamurthi, Comp. Physiol. Ecol. *5*, 326 (1980).
10 K. Raghavaiah, K. Satyanarayana, R. Ramamurthi and V. Chandrasekharam, Indian J. exp. Biol. *16*, 944 (1978).
11 N.V. Carroll, R.W. Longley and J.H. Roe, J. biol. Chem. *22*, 1583 (1956).
12 H.S. Tager, J. Markese, K.J. Kramer, R.D. Spiers and C.N. Childs, Biochem. J. *156*, 515 (1976).

Electrophysiological evidence for the existence of crossed nigrostriatal fibers

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Summary. A small number of neurones with electrophysiological properties of dopaminergic neurones and which were located in the pars compacta of the substantia nigra were antidromically activated by stimulation of the contralateral striatum. The characteristics of this response resembled closely those observed in other compacta neurones following ipsilateral striatal stimulation. These data indicate the presence of some crossed nigrostriatal fibers.

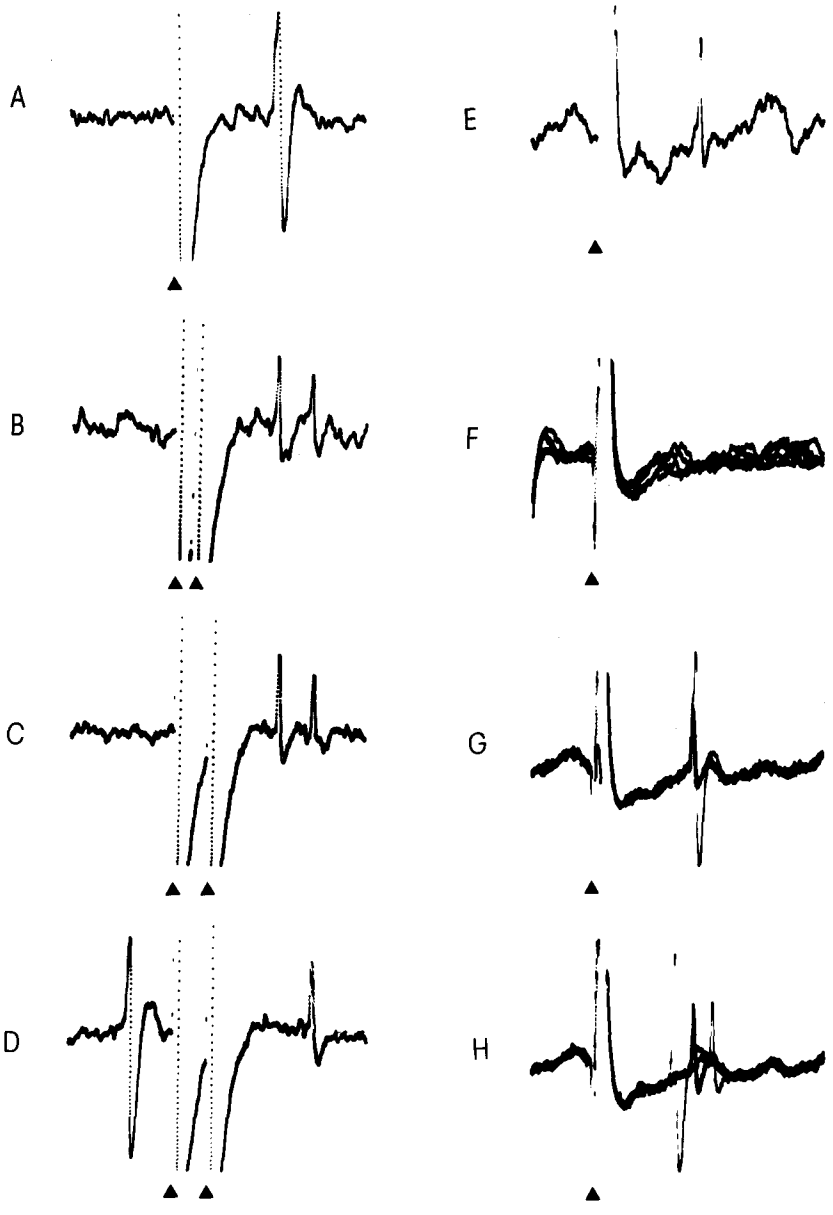
The dopaminergic nigrostriatal pathway is well documented anatomically, neurochemically and electrophysiologically and has received considerable interest regarding its possible dysfunction in extrapyramidal disorders such as Parkinsons's disease[3]. This pathway is generally regarded as being ipsilateral although some anatomical studies have suggested the presence of a small crossed constituent[4,5]. The present study was therefore undertaken to investigate whether any neurones located in the pars compacta of the substantia nigra could be antidromically activated by stimulation of the contralateral striatum.

Experiments were performed on male and female albino rats weighing approximately 200 g, anesthetized with urethane (1.2-1.4 g/kg^{-1} i.p.) or halothane (0.5-1.0% in oxygen). Extracellular recordings were obtained from nigral neurones using glass microelectrodes filled with 4 M NaCl or 0.5 M Na acetate and 2% pontamine sky blue dye, as described in detail previously[6,7]. The central cores of the ipsilateral and contralateral striata were stimulated (0.3 msec pulses, 0.05-3.0 mA delivered at 0.5-500 Hz) using stainless steel bipolar electrodes[6]. All electrode placements were confirmed histologically[6].

Recordings were obtained from 65 neurones in 18 rats which had the electrophysiological properties of dopaminergic nigrostriatal neurones[7,8] and which were predominantly located in the ventral pars compacta of the substantia nigra. Of these, 34 cells were antidromically activated following ipsilateral striatal stimulation, in the manner described previously[7]. None of these 34 cells were antidromically invaded by contralateral striatal stimulation. Of particular interest, however, was the finding that 2 of the cells, recorded in separate rats, that could not be antidromically activated by ipsilateral stimulation did respond antidromically to contralateral stimulation (fig.). The nature of this antidromic response was very similar to that seen with the ipsilateral projection in this and other studies[7-10]. Thus, these 2 cells had long latency antidromic spikes (13-19.5 msec) which were highly fractionated and there were frequent failures of the full antidromic action potential. In 1 cell there were considerable variations in the antidromic latency in response to both constant (fig. H) and altered stimulus strengths. This feature was often seen with the ipsilateral projection[9], presumably due to the axons being unmyelinated and highly branched. With both cells, the antidromic spike followed frequencies of stimulation of 250 Hz or more (fig. B), and invariably showed cancellation following collision with an appropriately timed spontaneous action potential (fig. D and F).

These results provide electrophysiological evidence that a small proportion of presumed-dopaminergic neurones located in the pars compacta of the substantia nigra project to the contralateral striatum. Anatomical studies have also suggested the existence of a minor crossed nigrostriatal projection[4,5,11], since in cat and rat a few neurones have been labeled in the pars compacta following injection of horseradish peroxidase or Evans blue into the contralateral striatum. Furthermore, labeling was not observed following injection of tracer into the overlying cortex, indicating that the pathway terminates in the striatum rather than just projects through it[5]. Although the 2 cells could only be antidromically activated by contralateral striatal stimulation it is possible that they projected to both striata and that the ipsilateral stimulating electrode was positioned in regions not innervated by that cell. Alternatively the projections of these neurones may be exclusively contralateral. The extent to which contralaterally projecting neurones also project to the ipsilateral striatum could probably best be resolved using double-label tracing techniques.

The existence of crossed dopaminergic nigrostriatal fibers has implications in studies in which unilateral manipulations of the substantia nigra have been employed in, for example, studies of extrapyramidal motor function[12]. They



Responses of compacta neurones to contralateral striatal stimulation. Records A-D are single oscilloscope sweeps of the 1st cell recorded. In *A*, a full antidromic spike was evoked with a latency of 13.5 msec in response to 0.2 mA striatal stimulation. (The position of the stimulus is shown by an arrow below the record and is followed by the stimulus artefact in this and subsequent records.) *B* illustrates frequency following of the initial segment (IS) spike in response to paired stimuli delivered at an interval of 3 msec. (Note the smaller amplitude and longer latency (15.5 msec) of the 2nd IS spike, presumably caused by a residual increase in conductance of the initial segment resulting from the 1st IS spike.) *C* illustrates frequency following to paired stimuli at a 5 msec interval (latency of 2nd IS spike was 14 msec). In *D*, the response to the 1st stimulus of the pair is absent due to collision with the action potential which occurred spontaneously just prior to stimulation. *E* is a single sweep from the 2nd cell illustrating occurrence of an antidromic IS spike with a latency of 13 msec. (Note the inflexion on the rising phase which may correspond to the axonal spike.) *F* illustrates 4 superimposed consecutive sweeps in which stimulation, at the same intensity as E, was triggered by a spontaneously occurring action potential (partially illustrated at the extreme left of trace). On all occasions the antidromic spike was absent due to collision by the spontaneous spike. *G* and *H* are both lower gain records of 5 consecutive superimposed sweeps of this same cell. In F, the IS spike invariably occurred at a constant latency (13 msec) and led to a full spike on one occasion. In G, the IS spike occurred at this latency on 3 occasions, at a longer latency (15.5 msec) on 1 occasion and was absent once due to the presence of the spontaneous action potential. In all records positivity is upwards and full spikes had amplitudes of approximately 4 mV. Duration of all traces was 40 msec.

may partly explain the contralateral reduction in striatal dopamine levels following unilateral pallidal lesion[13] and also contralateral changes in dopamine release following infusion of drugs into the nigra[14]. Presumably other pathways are also involved in the complex changes in dopamine release in both striata and nigra following unilateral administration of drugs to one of these structures. Indeed, striatal stimulation was sometimes observed to result in the orthodromic excitation and/or inhibition of neurones in the contralateral pars compacta and reticulata (unpublished observations), suggesting the presence of other crossed, but probably polysynaptic, projections.

In conclusion, this report has demonstrated the existence of neurones which project to the contralateral striatum but in all other respects are similar to ipsilaterally projecting, nigrostriatal dopamine neurones. Further studies are required to determine the exact extent and functional significance of this contralateral nigrostriatal projection.

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3 A. Dray, Neuroscience *4*, 1407 (1979).
4 G.J. Royce, Brain Res. *153*, 465 (1978).
5 B. Fass and L.L. Butcher, Neurosci. Lett. *22*, 109 (1981).
6 G.L. Collingridge and J. Davies, Neuropharmacology *18*, 193 (1979).
7 G.L. Collingridge and J. Davies, Brain Res. *212*, 345 (1981).
8 P.G. Guyenet and G.K. Aghajanian, Brain Res. *150*, 69 (1978).
9 G.L. Collingridge, T.A. James and N.K. MacLeod, Experientia *36*, 970 (1980).
10 J.M. Deniau, C. Hammond, A. Riszk and J. Feger, Exp. Brain Res. *32*, 409 (1978).
11 J.A. Pearson and P. Pinkhasik, personal communication.
12 C.J. Pycock, Neuroscience *5*, 461 (1980).
13 Z. Hahn, L. Lenard and Z. Karadi, Neurosci. Lett. *13*, 91 (1979).
14 V. Leviel, A. Cheramy and J. Glowinski, Nature *280*, 236 (1979).