

Neurotransmitter Receptors in Fetal Tissue Transplants: Expression and Functional Significance

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ABSTRACT

Numerous studies have examined receptor expression in neural transplants and their possible role in transplant-induced functional recovery from lesion-induced deficits. Herein we attempt to summarize the results of these studies, especially those from studies involving striatal transplants. Autoradiographic studies indicate that dopamine D₁ and D₂, muscarinic, cholinergic, 5-HT₂, opiate μ , β adrenergic and cholecystokinin (CCK) receptors are present in striatal transplants. Many of these receptors are present regardless of the transplant location and surrounding environment. This suggests that the expression of these receptors is determined by intrinsic properties of transplanted tissue, and is independent of transplant location and environment. Some transplant receptors, such as dopamine D₁ and D₂ and muscarinic receptors in striatal transplants, or 5-HT₂ receptors in cortical transplants, display a patchy distribution which is dissimilar to that in the corresponding adult host tissue. This manuscript discusses this "abnormal" receptor distribution and possible explanations. Electrophysiological studies have indicated that some of the transplant receptors respond to physiological and pharmacological stimulation, suggesting that they are functional. However, the association of receptor expression with behavioral recovery is uncertain. The expression of neurotransmitter receptors in neural transplants may not be essential for the

functional recovery associated with trophic mechanisms. However, neurotransmitter receptors may play an important role when functional recovery requires neuroanatomical integration between the host brain and the transplanted tissue.

KEY WORDS

dopamine, serotonin, behavior, muscarinic acetylcholine receptors, fetal tissue grafts, *c-fos*

INTRODUCTION

Numerous studies have demonstrated that fetal brain tissues can survive transplantation and develop some neuroanatomical and histochemical features characteristic of mature tissues /7,22,28/. Neural transplants can also ameliorate many behavioral abnormalities induced by neurotoxic lesions in animal models of Parkinson's disease and Huntington's disease /2,16,17,18,27,42,49,51,55/. For example, transplants of fetal striatal tissue into excitotoxin-lesioned striatum have been shown to ameliorate the striatal lesion-induced abnormalities in spontaneous behaviors, such as locomotor activity /45,50/ and skilled paw reaching behaviors /16/, and also drug-induced deficits, including apomorphine-induced rotational behavior /16,40, 43/, apomorphine and amphetamine-induced locomotion /11,14,49/ and haloperidol-induced catalepsy /19/. In addition, striatal transplants have been reported to produce recoveries of lesion-induced neurochemical deficits, such as for choline acetyltransferase (CAT) and gamma-aminobutyric acid (GABA) /28/.

Recent experiments have focused on the possible mechanisms by which neural transplants promote

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behavioral recovery. One hypothesis is functional anatomical integration between transplant and host. Some specific afferent and efferent connections between transplants and host have been reported /2,4,45,63-65/. If these anatomical connections are important for transplant-induced recovery, neurotransmitter receptors will be required to mediate these effects, since they are necessary for synaptic signal transduction.

Several groups have studied receptor expression and possible function in fetal striatal tissue transplants /13,14,24,28,35,38,40,43,62/. Herein we attempt to summarize the findings in this area and discuss the development of receptors in transplants and their possible role in transplant functions.

RECEPTOR EXPRESSION IN NEURAL TRANSPLANTS

Several groups have demonstrated that fetal striatal tissue can survive and express a variety of receptors and transmitter specific neuronal markers. The biochemical markers for intrinsic neurons identified in striatal transplants include acetylcholinesterase (AChE) /22,28,50,59/, met-enkephalin (met-ENK), substance P (SP), somatostatin (SS), cholecystokinin (CCK) and neuropeptide Y (NPY) /22,28/.

Autoradiographic studies have demonstrated that dopamine D₁ and D₂ muscarinic cholinergic, 5-HT₂, opiate μ and δ , adrenergic β and CCK

TABLE 1

Summary of the expression of neurotransmitter receptors and second messenger systems in fetal striatal tissue transplants

Study	Donor	Host	Months Post-Graft	Ligand/Receptor	Result	Functional Correlation
Beresford et al, (1)	E13-15 cell suspension			[¹²⁵ I]CCK-8/CCK	(+), patchy	Reduction of rotational behavior
Deckel et al, (11)	E17-18 whole cell suspension	Female rat with KA lesion	6	Spiperone/D ₂ dopamine	(-)	Receptor density inversely correlated with the locomotor hyperactivity following amphetamine and apomorphine
Deckel et al, (12)	E18	Adult female rat with KA lesion	9	[¹²⁵ I]cyanopindolol +ICI-89406/ β_1 [¹²⁵ I]cyanopindolol +ICI-118551/ β_2	(+) (+) the same density as in host striatum	
Deckel et al, (13)	E17 cell suspension	Adult female rat with KA lesion or without	8	NMS+carbachol/M ₁ NMS+atropine/M ₂	(+) reduced density (+) increased density	Receptor density correlated with the sensorimotor and alternation task, but not correlated with locomotor measurement, inversely correlated with behavior following amphetamine and apomorphine
Deckel et al, (14)	E19 cell suspension	Adult female rat with KA lesion or without	6	Spiperone/D ₂	(+), patchy	Receptor density inversely correlated with behavior following amphetamine and apomorphine injection

TABLE 1 (cont.)

Study	Donor	Host	Months Post-Graft	Ligand/Receptor	Result	Functional Correlation
Helm et al, (24)	E15-16 cell suspension	Adult rats with KA lesion	4-6.5	SCH23390/D ₁ Spirerone/D ₂ QNB/muscarinic Hemicholinium/ high affinity choline uptake site Forskolin/ adenylyate cyclase Phorbol 12,13-dibutyrate/ protein kinase C	(+), patchy (-) (+), even (-) (+), patchy (+), evenly throughout the graft	
Isacson et al, (28)	E14-15 cell suspension		6	Spiperone/D ₂ Diprenorphine/ opiate PBCM/muscarinic	(+), patchy (+), patchy (+), even	
Lanca et al, (33)	E12-19 cell suspension	Rat pups and young adult	1-3	Etorphine/opiate Spiperone/D ₂	(+), patchy (-)	
Lu et al, (36)	E15-17 solid tissue	Adult male rat with intact striatum	1.5 - 15	SCH23390/D ₁ Spirerone/D ₂ Ketanserin/5-HT ₂ QNB/muscarinic	(+), patchy (+), patchy (+), patchy (+), even	
Mayer et al, (38)	E15 cell suspension	Adult female rat with ibotenic acid lesion	3	SCH23982/D ₁ Sulpiride/D ₂	(+), patchy (+), patchy	
Norman et al, (43)	E17 solid tissue	Male adult rats with KA lesion	2.5	SCH23390/D ₁ Spirerone/D ₂ Forskolin / adenylyate cyclase	(-) (-) (-)	No correlation with the recovery of the lesion-induced rotational behavior

"(+)" -- indicates the presence of receptors in the transplants

"(-)" -- indicates the absence of receptors in the transplants

NMS = N-Methylscopolamine

PBCM = Propylbenzilylcholine mustard

receptors are present in striatal transplants /1,11,12, 13,14,24,28,33,36,38/ (results are summarized in Table 1). These receptors are normally present in adult rat striatum /21/. The density of D₁ dopamine receptors in striatal transplants was reportedly about 2 to 3-fold higher than that of dopamine D₂ receptors /38/, which is similar to that in normal striatum. The dopamine D₁ and D₂ and muscarinic receptors were present in striatal transplants as early as 6 weeks after transplantation /36/. In most reports, the receptors were observed in striatal transplants about 3-11 months after the implantation (see Table 1).

However, the autoradiographic studies have also shown some conflicting findings. Deckel *et al.* /11/ initially reported the absence of dopamine D₂ receptors in striatal transplants. Similarly, Norman *et al.* /43/ reported an apparent lack of D₁ and D₂ dopamine receptors within the transplant. However, subsequent studies /36/, using transplants into non-lesioned adult rat brain, reported the patchy distribution of dopamine D₁ and D₂ receptors, muscarinic receptors and the presence of 5-HT₂ receptors in the striatal transplants. A recent study by Helm *et al.* /24/ reported the absence of dopamine D₂ receptors in 4 and 6.5 month-old transplants, which was consistent with the studies of Norman *et al.* /43/ and Deckel *et al.* /11/. Dopamine D₁ receptors were also found to be absent at 4 months, consistent with the results of Norman *et al.* /43/, but were reported to be present in sparse patches at 6 months post transplant /24/.

When neurotransmitter receptors are found to be expressed in transplanted fetal tissue the distribution is often patchy. Less clear is the reason for the apparent lack of or inconsistent receptor expression in some studies. This relative lack of receptors in transplants cannot be due to technical problems with the autoradiographic assay procedure as binding of the radioligand to appropriate receptors in adjacent host tissues is apparent. Furthermore, this inconsistency is not due to the different forms of embryonic tissue transplanted, such as cell suspension vs. tissue block, because in either case, both positive and negative results have been reported. Additionally, differences in receptor expression between studies are apparent even from the same laboratories. Deckel *et al.*, although initially reporting a lack of D₂ dopamine receptors,

subsequently observed D₂ dopamine receptors /14/. A lack of D₁ and D₂ receptors was observed in some studies /43/ but subsequent studies using a similar protocol of striatal transplants into non-lesioned adult rat brain observed the patchy distribution of both D₁ and D₂ dopamine receptors /36/.

EXPRESSION OF TRANSPLANT INTRINSIC RECEPTORS MAY BE INDEPENDENT OF TRANSPLANT LOCATION AND ENVIRONMENT

Normal striatum has relatively high levels of dopamine D₁ and D₂ and muscarinic acetylcholine receptors, high to moderate levels of adrenergic α and β, 5-HT and opiate receptors /9,21/. Expression of receptors in neurons during normal development may depend on genetic information. Additionally, environmental cues, such as target innervation, hormonal levels, etc., may also play an important role. Studies on the expression of neurotransmitter receptors in transplants placed in different locations within the brain or into the anterior chamber of the eye, provide information which may reflect the influence of the local environment. For instance, when striatal transplants were placed either into striatum (homotopic location) or globus pallidus or substantia nigra (ectopic locations), dopamine D₂, muscarinic and opiate receptors, in addition to the neurochemical markers AChE, SP, met-ENK and NPY, were expressed in the tissues placed in all locations. In addition, the distribution, uniform in the case of muscarinic receptors and patchy in the case of the other receptors and the neurochemical markers, was independent of the location of the transplant /28/. Even when striatal transplants were placed in the lateral ventricle in which the transplants were relatively isolated from anatomical interactions, they were able to express D₁ and D₂ dopamine and muscarinic receptors /36,38/. Similarly, many types of transplants can develop appropriate neuronal neurochemical markers and receptors when they are transplanted into the anterior chamber of the eye /44/. In addition, fetal striatal transplants expressed the same types of receptors when they were placed either in excitotoxin lesioned striatum or intact striatum /13,14,28,36/.

Neurotransmitter receptors have also been identified in other types of transplants, for example, α and β adrenergic receptors in intraocular cerebellar transplants /20/, β adrenergic receptors in fetal cortical and cerebellar tissues transplanted into cortex /34/, muscarinic and 5-HT₂ receptors in ventral mesencephalic and cortical tissues transplanted into striatum /36/. Therefore, these data suggest that the expression of appropriate receptors and of some phenotypic neurochemical markers in transplants is largely determined by intrinsic environmental or genetic information rather than extrinsic environmental factors.

However, this may not be true for certain receptors which may depend on extrinsic conditions, such as anatomical connections from the host, for their expression and normal development. The expression of opiate μ receptors in homotopic striatal transplants has been reported to require innervation by host dopaminergic fibers /54/. Opiate μ receptors have been reported to be located on dopaminergic terminals originating from the substantia nigra /54/. Therefore, this receptor maybe extrinsic to striatal tissue and its expression within intrastriatal transplants may reflect the ingrowth of dopaminergic terminals from the host.

THE DISTRIBUTION OF RECEPTORS WITHIN TRANSPLANTS IS DISSIMILAR TO THAT IN HOST

Despite the presence of receptors with densities sometimes similar to those observed in the host, the distribution of receptors in transplants is clearly different from that in the adult host. Some receptors are found in very discrete areas within the transplant often in relatively high densities, while in other areas of the transplant the receptors are often absent. This patchy receptor distribution characterizes dopamine D₁ and D₂, and opiate μ receptors in striatal transplants /14,28,36,38,62/. The distribution of muscarinic receptors has been described as patchy or non-uniform in some studies /13,36/ but more uniform in other studies /28/. 5-HT₂ receptors have been reported to be evenly distributed throughout striatal transplants but patchy in cortical transplants /36/. The patchiness of the distribution of D₁ and D₂ dopamine and muscarinic receptors in fetal striatal transplants as well as the opiate μ receptor is

dissimilar to that in the host striatum. These patches of relatively high receptor density have been reported to correspond to the patches in the striatal transplants that are rich in AChE, met-ENK, substance P, somatostatin and tyrosine hydroxylase /28,66/. It was initially suggested that this patchy distribution of receptors and neurochemical markers may reflect the compartmentation known as striosomes normally present during development and in mature striatum /28,33/. However, Graybiel *et al.* /22/ suggested that these high density patches rich in a variety of the neurochemical markers may have achieved a phenotype resembling normal developing and mature striatum while the histochemical features of the low density patches were similar to immature striatum and non-striatal tissues. The possibility was suggested that some globus pallidus, basolateral amygdala and cortical tissue was included during the dissection of fetal striatum due to the proximity of these tissues to the dissection area /22,28/.

The purity of transplanted fetal tissues can be more easily maintained using fetal cortex as this tissue is relatively large and clearly differentiated from other areas of the fetal brain. In cortical transplants clear lamination of 5-HT₂ receptors which was observed in the host cortex was not seen. Instead, dispersed patches of 5-HT₂ receptors having relatively high density were intermingled with low density areas /36/. From the corresponding Nissl stained sections it was evident that this patchiness of receptor density was not due to uneven density of neurons within the transplant. Furthermore, the muscarinic receptors in the same transplant were evenly distributed. It is, therefore, possible that the high density patches of 5-HT₂ receptors were caused by clustering of the cortical neurons that express high densities of 5-HT₂ receptors. These high density patches may have intermingled with cortical neurons expressing low densities of 5-HT₂ receptors, which in some degree resembled the normal cortex, but with a disrupted laminar organization. Alternatively, it is possible that the neurons in the high receptor density regions received a signal which stimulated the expression of 5-HT₂ receptors while the neurons in the low receptor density region did not receive such a signal. However, there have been no systematic

studies to evaluate these hypotheses. These data suggest that the patchy distribution of some neurotransmitter receptors, at least within cortical transplants, is not due to the impurity of the transplanted fetal tissue. Rather, although some phenotypes of mature tissues can be expressed in transplanted tissue, certain essential elements required for complete normal organization of cells or the development of receptors and other neurochemical markers within the transplanted tissue may have been missing or inadequate.

PHYSIOLOGICAL FUNCTION OF RECEPTORS IN TRANSPLANTS

The physiological function of receptors in striatal transplants has also been studied. Wichmann and Starke /62/ have studied the effect of striatal transplant-derived dopamine receptors and muscarinic and opiate receptors on acetylcholine release from transplants by measuring [³H]acetylcholine efflux from slices of transplanted striatum. They reported that the activation of dopamine D₂, muscarinic and opiate δ receptors by specific receptor agonists inhibited [³H]acetylcholine release from slices of transplanted striatum which resembled the effect in normal striatum. This effect increased with increasing concentration of the agonists, and was abolished by appropriate receptor antagonists. The results indicated that these receptors had similar functions to the corresponding receptors in normal striatum with regard to modulation of acetylcholine release. In addition, electrophysiological recording has revealed that the synapses formed between transplant and host can be functional. The response observed in transplants by stimulation of the host neurons /2,25,48,61/ is presumably mediated by neurotransmitters from the stimulated host neurons acting on neurotransmitter receptors present on the transplanted neurons. Further evidence of functional receptors mediating physiological activities comes from studies showing that α and β adrenergic receptors in intraocular cerebellar transplants mediated the electrophysiological effect of norepinephrine on Purkinje neurons /20/. Furthermore, data from intracerebral dialysis from intrastriatal nigral transplants indicated

that dopamine autoreceptors in nigral transplants may mediate the autoregulation of dopamine release and metabolism /57/. A methamphetamine-induced stimulation of GABA release in the globus pallidus and substantia nigra was also restored by striatal tissue grafts into excitotoxin-lesioned striatum /54/, suggesting that functional dopaminergic modulation within the transplanted tissue of GABA output neurons was re-established. These dopamine receptors within both nigral and striatal transplants may develop functions similar to those in mature tissue.

In normal brain, some neurotransmitter receptors are associated with the second messenger system, adenylate cyclase /56/. Therefore, the presence of second messenger systems in transplanted tissues may be an indicator of functional receptors. [³H]Forskolin binding has been used to identify the stimulatory guanine nucleotide regulatory subunit/adenylate cyclase complex and its association with the D₁ dopamine receptors in transplants /24,43/. Norman *et al.* /43/ demonstrated a relative deficit of [³H]forskolin binding sites corresponding to the lack of D₁ dopamine receptors in the striatal transplants at 12 weeks post transplant. A recent study by Helm *et al.* /24/ reported the presence of a patchy distribution of [³H]forskolin binding sites in 6 month-old transplants which was similar to the D₁ dopamine receptor patches in the striatal transplant, again suggesting their possible association. [³H]Phorbol ester binding to protein kinase C, another second messenger system, was present in the transplanted striatal tissue, but in contrast to the dispersed patches of [³H]forskolin binding, protein kinase C was very prominent throughout the transplant /24/. The available data suggest that D₁ dopamine receptors when present in striatal transplants are associated with the presence of adenylate cyclase and protein kinase C, though not necessarily in a normal stoichiometric relationship. However, there are no studies to date to determine whether receptor agonists elicit activation of second messenger systems within transplants. Such studies would be technically difficult. However, indirect evidence might come from the measurement of the expression of immediate-early response gene products /15/. The expression of such proto-

oncogenes, for example *c-fos*, can be stimulated by a number of neurotransmitters and receptor agonists. For example, D-amphetamine or cocaine elicits a marked expression of *c-fos* in rat striatum through indirect activation of dopamine receptors, especially of the D₁ subtype /23,47/. Therefore, the amphetamine-induced activation of *c-fos* in fetal tissue transplants might indicate the presence of functional monoaminergic synapses in the transplanted tissues. In cortical and striatal tissues transplanted into rat striatum most of the dopaminergic innervation would be from the host. The expression of *c-fos* in the transplants could be indicative of functional D₁ dopamine receptors on the transplanted neurons. Amphetamine was able to stimulate the expression of fos-like immunoreactivity in fetal striatal grafts transplanted into intact adult striatum /37/. This amphetamine-induced stimulation of *c-fos* was abolished by dopamine deafferentation of the host striatum /37/ implying that functional innervation of the transplanted tissue mediated the response. Furthermore, this same study found that the directly acting dopamine receptor agonist, apomorphine, was able to stimulate the expression of fos-like immunoreactivity in the intrastratal graft following the dopamine deafferentation. Interestingly, apomorphine is able to stimulate the expression of *c-fos* in dopamine deafferented, but not in intact rat striatum. Presumably, this is due to a requirement for supersensitive dopamine receptors for the apomorphine-induced expression of *c-fos*. Therefore, the data of Mandel *et al.* /37/ implied that dopamine receptors were present in the transplant and had the same pharmacological characteristics and were under the same regulatory mechanisms as were the receptors in the adult striatum.

Although muscarinic cholinergic receptors develop in fetal striatal grafts this population of receptors may consist of an abnormal ratio of pharmacologically defined receptor subtypes. Deckel *et al.* /13/ reported that the number of putative M₁ receptors was reduced while the number of putative M₂ receptors was increased. This may indicate some abnormality of receptor development which in turn may cause abnormal signal transduction. However, the significance of

these findings is unclear as the use of agonist displacement of non-selective muscarinic antagonists can be complex. It was assumed /13/ that the agonist displaceable [³H]N-methyl scopolamine (NMS) binding represented a distinct muscarinic receptor subtype (M₂) while the remaining binding of the [³H]NMS represented the M₁ muscarinic receptor. However, the M₁ muscarinic receptor subtype has also been demonstrated to have both high and low affinity agonist states /39/. Furthermore, the binding of the quaternary antagonist [³H]NMS is complex /41/, making such agonist displacement studies even more difficult to interpret. It is more likely that the 'M₂ receptor' represented the high affinity agonist states of a number of muscarinic receptor subtypes rather than a single population of pharmacologically distinct receptors. Conversely, the 'M₁ receptor' would represent the low affinity agonist states of these same multiple receptors. The reported changes in agonist competition would indicate that the number of muscarinic receptors in the high affinity agonist state was increased in the transplant relative to the adult host. As the agonist affinity states are determined by coupling to guanine nucleotide regulatory subunits /39/ there may be alterations in cholinergic signal transduction mechanisms in the transplanted tissue.

There was a lack of high affinity choline uptake sites in striatal transplants in spite of the presence of a high density of muscarinic cholinergic receptors, suggesting that few functional cholinergic terminals were present in the transplants /24/. Furthermore, the development of alpha-bungarotoxin binding sites in fetal tectum transplanted into rat midbrain occurs independently of inputs from the host brain or functional cholinergic innervation /58/. Thus, the functional significance of the muscarinic or putative nicotinic receptors present in the transplants is not clear.

Studies also revealed that some transplant receptor function is conditional and dependent on specific host-transplant anatomical connections and integration. For example, opiate κ receptor agonists failed to enhance the stimulation-evoked acetylcholine release in slices of transplants /62/. This effect was observed in normal striatal slices which depended on a dopaminergic input to the

cholinergic cells. This suggests that opiate κ receptor function is dependent not only on the expression of the receptor but also on the integration of the host dopaminergic system with the transplanted tissue. However, it is not clear from these studies whether this dependence of opiate κ receptor-mediated responses on dopaminergic innervation reflects the localization of these receptors on dopaminergic fibers as suggested for the opiate μ receptor /54/.

The response of physiologically functional receptors within transplants can be inferred from electrophysiological studies and from the agonist-induced modulation of transmitter release from transplant slices. However, there are also some receptors present in regions of transplants which do not appear to have the appropriate neuronal innervation. Therefore, the functional relevance of these receptors under *in vivo* conditions is unclear unless they can be activated by neuroactive compounds diffusing from non-local sources.

POSSIBLE FUNCTION OF RECEPTORS IN PROMOTING BEHAVIORAL RECOVERY

Striatal transplants have been demonstrated to be able to reverse many behavioral deficits induced by striatal excitotoxin lesions /2,16,27,42,51/. However, the association between the expression of receptors in transplants and transplant-induced behavioral recovery from lesion-induced deficits is uncertain. For example, it has been reported that the transplant-induced amelioration of apomorphine-induced turning behavior following unilateral excitotoxin lesions of the adult striatum appeared to be independent of the presence of receptors in the transplant /43/. Whether or not transplant-derived receptors play a role in behavioral modulation may be dependent on a variety of factors, such as the degree of integration of the receptors with appropriate host circuitry, and/or whether the function mediated via the particular receptors requires local circuits or specific anatomical connections with the host. It is also possible that neurotrophic factors released from transplants may be at least partially responsible for early recovery of drug-induced rotation behavior. The recovery of

unilateral excitotoxin lesion-induced rotational behavior was reported as early as 5 weeks following transplantation /40,42,43/. At this time, there is no clear evidence for substantial connectivity between host and transplant /59/. Therefore it is possible that trophic factors or other agents may diffuse from the transplant into surrounding host tissue and promote regenerative activity of the remaining host tissue. Indeed, it has been suggested that transplants of adrenal medulla into dopaminergic deafferented rat striatum can induce sprouting of the remaining host dopaminergic fibers, presumably via a trophic mechanism /3/. Trophic factors have also been demonstrated to be produced in the brain in response to injury, and transplants of fetal tissues have been suggested to restore function in part by providing trophic support to the remaining host tissues /5,6/. Receptors within the transplant may not be essential for this putative aspect of transplant function. However, for recovery of other motor tasks, for example, skilled paw reaching in rats /16/, higher levels of anatomical and functional integration, including receptors, may be required. It has been demonstrated that many transplant-host connections were established in the same patches in which a high density of receptors were present and that were also rich in appropriate neurochemical markers /28/. Therefore, it is conceivable that in these areas the receptors in transplants may actively modulate the recovery of more complex host functions.

In addition to host modulation of receptors in the transplanted tissue, neurotransmitter receptors in the host brain can be modulated by transplanted tissue. For instance, intrastratal ventral mesencephalic transplants were reported to be able to correct dopamine receptor supersensitivity in the striatum following lesion of the nigro-striatal dopaminergic pathway in rats /10,17,46/. Interestingly, in the post-mortem striatum of a patient with Parkinson's disease who had received an autologous transplant of adrenal medulla /26,31/, a marked decrease in the levels of 'supersensitive' D₁ dopamine receptors was observed returning the receptor levels to those observed in control striatum /31/. A decrease in the elevated levels of D₂ dopamine receptors was also observed in specific regions of the caudate, though the effects were not

as great as observed for D₁ dopamine receptors /31/. This relative normalization of dopamine receptors was restricted to the area immediately surrounding the surviving transplanted cells where there was also an increase in [³H]mazindol binding indicating an increased density of dopaminergic terminals. Thus, the localized increase in dopaminergic innervation of the human striatum (possibly due to graft-induced sprouting of remaining host dopaminergic fibers) also appears to elicit changes in levels of dopaminergic receptors in the host striatum.

This relative normalization by fetal transplants of neurotransmitter receptors in the host brain is not restricted to striatum. Cholinergic deafferentation of the rat hippocampus elicits a location-specific increase in muscarinic receptors. Following transplantation of fetal septum into the lesioned hippocampus, an increase in cholinergic markers is observed concomitant with a normalization of the levels of muscarinic receptors /8,29,30,52/.

There is also some indirect evidence of fetal tissue transplants modulating receptor sensitivity in the unlesioned rat striatum. Transplantation of various fetal tissues into the intact adult striatum elicited a hyporesponsiveness to most locomotor behaviors induced by amphetamine or by doses of apomorphine which predominantly activate postsynaptic dopamine receptors /35/. Furthermore, the transplanted rats displayed significantly greater catalepsy than normal rats following the injection of the dopamine receptor antagonist haloperidol /35/. These data are consistent with a decreased sensitivity of postsynaptic dopamine receptors. These effects were produced by transplants of different fetal tissues not all of which expressed dopamine receptors /36/. This suggested that the transplants produced a common effect in the host striatum. A hypersensitivity to the locomotor inhibiting effects of a lower dose of apomorphine which is relatively selective for autoreceptor activation was observed /35/. This suggested that an increase in the sensitivity of presynaptic dopamine receptors could be elicited in the host striatum by transplants. That the transplanted tissue is capable of modulating the function of the host brain in this way demonstrates an important principle of neuroplasticity in adult brain. Clearly transplanted

tissues may be capable of inducing many neurochemical and physiological responses in adult host brain. Thus, functional recovery of lesion-induced deficits following neural transplantation might also be produced by transplant-induced receptor plasticity of the adult host brain.

Receptors are key components of signal propagation and also important elements of neuroplasticity /32/. Long term changes in the concentration of transmitters may result in changes in the sensitivity of receptor-mediated responses. Transplants of neuronal tissue into host brain will introduce new tissue into the host which may produce a variety of factors, including neurotrophic factors and neurotransmitters. These transplant-derived factors may elicit a reorganization of the host tissue. Alternatively, the host may also influence transplant function by modulating its neuronal activity, possibly via changes in receptor sensitivity.

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