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Dopamine-glutamate interactions in the basal ganglia

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Summary. In an attempt to formulate a working hypothesis of basal-ganglia functions, arguments are considered suggesting that the basal ganglia are involved in a process of response selection i.e. in the facilitation of "wanted" and in the suppression of "unwanted" behaviour. The meso-accumbal dopamine-system is considered to mediate natural and drug-induced reward and sensitization. The meso-striatal dopamine-system seems to fulfill similar funcions: It may mediate reinforcement which strengthens a given behaviour when elicited subsequently, but which is not experienced as reward or hedonia.

Glutamate as the transmitter of the corticofugal projections to the basal ganglia nuclei and of the subthalamic neurons is critically involved in basal ganglia funcions and dysfunctions; for example Parkinson's disease can be considered to be a secondary hyperglutamatergic disease. Additionally, glutamate is an essential factor in the plasticity response of the basal-ganglia. However, opposite to previous suggestions, the NMDA-receptor blocker MK-801 does not prevent psychostimulant- nor morphine-induced day to day increase (sensitization) of locomotion. Also the day to day increase of haloperidol-induced catalepsy was not prevented by MK-801.

Keywords: Basal ganglia loops – Reward – Sensitization – NMDA receptor – Parkinson's disease

The basal ganglia circuitry

Phylogenetically the basal ganglia (BG) have evolved from a purely descending system (in primitive vertebrates) to a system forming loops: In non-mammalian species, the striatum receives glutamatergic input mainly from the thalamus and by way of the other BG nuclei projects back to the thalamus. With the phylogenetic increase in the volume of the cerebral cortex, loops are formed by neurons projecting from the cortex to the striatum and the through the other BG- nuclei and the thalamus back to the cortex. However, still in primates, the BG are also part of a descending system using the substantia nigra pars reticulata as the output station.

According to our current view, (for review see Schmidt and Kretschmer, 1997) a cortical signal reaching the striatum, is transmitted to the thalamus by way of two (direct loop) or three (indirect loop) GABAergic neurons. Thus a cortical signal produces either disinhibition or inhibition of the thalamus and in turn increases or decreases the thalamo-cortical activity. It is a matter of actual debate whether by virtue of this, the BG are involved in a process of evaluation that results in suppression of "unwanted" and in facilitation of "wanted" behaviour. Some formerly unexplainable electrophysiological results find an explanation in this assumption: While direct stimulation of the striatum does not elicit distinct behavioural responses it can facilitate or inhibit otherwise elicited behaviour.

Dopamine

The information flow through the striatum is modulated by meso-striatal dopamine (DA) neurons.This DA-pathway is phylogenetically older than the cortico-striatal glutamte (GLU) releasing pathway: It is found at an evolutionary level at which a neocortex has not yet evolved.

The DA innervations of the dorsal and of the ventral striatum (nucleus accumbens) do not seem to transmitt fast sensory or motor information, rather they seem to signal aspects of reinforcement and reward; here the hypothesis is considered that DA plays a decisive role in the evaluation of what is "wanted" or "unwanted".

In the nucleus accumbens, DA mediates reward, experienced as hedonia or euphoria

The neurons from the ventral tegmental area to the nucleus accumbens are part of a system that enables the individuum to experience what is called reward, hedonia or euphoria. These neurons are the target of many drugs of addiction; to which extend, is a matter of discussion, but at least amphetamine and cocaine act by way of this projection. The DA released by these neurons plays a role in sensitization, addiction and, after drug withdrawal, in craving (Wise, 1996).

In the dorsal striatum, DA mediates reinforcement, not experienced as hedonia

The dorsal striatum is discussed mainly in connection with motor control. A DA hypoactivity results in hypokinesia or akinesia, (this is the case in Parkinson's disease) while DA overactivity results in hyperkinesia. In order to explain this, and mainly in connection with Parkinson's disease, a lot of ideas and hypotheses have been presented about DA, the dorsal striatum and the control of motor behaviour. However, no generally accepted agreement about the functions of the dorsal striatum has been achieved.

Based on the ideas of Beninger (1983) and Schultz et al. (1995) the following hypothesis will be considered here: DA does not influence what

actually happens, but indicates how "good" or how "bad" the outcome of stimulus-behaviour connection was in relation to the expectations of the individuum. In contrast to DA release within the nucleus accumbens, this positive or negative reinforcement is not experienced as hedonia or anhedonia respectively. The following arguments and findings support, or at least are in accordance with the proposed hypothesis: DA neurons have a slow conductance velocity and thus, DA is released after the execution of a movement. But after training, DA may also be released in anticipation of a reward (Ljungberg et al., 1991). Further, in the striatum LTP and LTD have been observed which may be the underlying mechanisms for learning, reinforcement or extinction (Calabresi et al., 1996).

A corollary of these assumptions is that a "good" behavioural outcome enhances DA release and strenghtens a given behaviour when elicited subsequently. Though we can not estimate what is good or what is wanted. Ljungberg et al. (1991, 1992) clearly showed, that DA neurons fire in relation to attentional and incentive processes. Stimulus-behaviour connections of high biological significance most reliably enhanced the activity of DAergic neurons. As soon as a response becomes a routine or is performed in a habit like manner, DAergic neurons decrease their responsiveness. The characteristics of the DA system are also expressed by the spiny neurons upon which the DA neurons impinge. Data have been collected indicating that the spiny neurons of the striatum are able to recognize current contextual patterns that have, in the past, preceeded certain salient events such as the delivery of a food reward (Houk et al., 1995, p. 98). The view that DA facilitates behaviour also nicely fits to the well known phenomenon that experimentally increased DA-activity results in sensitization not only in the nucleus accumbens but also in the dorsal striatum (Tzschentke and Schmidt, 1996); and that excessively increased DA-activity results in stereotypy.

A second corollary is that a "bad" behavioural outcome reduces DA release and will weaken a given behaviour when elicited subsequently. Experimentally reduced DA-activity results in extinction like decrease of behaviour (Beninger, 1983). With decreasing DA activity, behaviours disappear in the following order of sucession:

Spontaneous, internally guided behaviour, conditioned behaviour, externally guided behaviour and key-stimulus-fixed action pattern connections (Schmidt, 1984); the latter ones being the most stable behaviours which can be elicited in even completely akinetic animals (Wegener et al., 1988).

Glutamate

Glutamate (GLU) is the transmitter of most, perhaps of all cortio-fugal neurons and thus, also most BG nuclei receive a GLUergic input. The striatum, as the main input station, receives GLUergic neurons from the whole cortex, but also about 10–15% from the thalamus. In the striatum, a well balanced equilibrium between inhibitory DA effects (at D2 receptors) and excitatory GLU effects (at NMDA receptors) does exist. A DA deficit, as it occurs in Parkinson's disease, results in overactivity of the striato-pallidal

neurons. By means of local infusions of GLU receptor-antagonists into the striatum it has been shown that GLU through NMDA (but not through AMPA receptors) drives these striato-pallidal neurons and thus NMDA receptor-antagonists are able to reverse parkinsonian symptoms (Schmidt, 1986; Schmidt and Bubser, 1989; Chesselet, 1996).

Plasticity in the generation of parkinsonian symptoms

GLU also plays a key role in the process of sensitization i.e. the progressive augmentation of specific behaviour (mostly hyperactivity) elicited by the repeated administration of psychostimulants such as amphetamine, cocaine or other addictive drugs. It has been argued repeatedly that the NMDA-receptor antagonist MK-801 blocks the sensitization to the psychomotor stimulant properties of amphetamine, cocaine, morphine and apomorphine (for literature see Wise et al., 1996):

Studies with psychostimulants in combination with MK-801 are sometimes difficult to interpret since MK-801 by itself also has DA-releasing as well as behavioural stimulant properties. Therefore we designed an experiment based on the following consideration: It is well known that rats when repeatedly injected with the neuroleptic drug haloperidol and tested subsequently in a catalepsy test (horizontal bar, vertical grid) develop a day to day increase in catalepsy (akinesia and rigdity). Therefore we tested whether the progressive increase in catalepsy can be considered as a special form of sensitization and whether it can be blocked by MK-801.

One group of rats treated with haloperidol plus saline produced a day to day increase in catalepsy during 7 days. A second group receiving haloperidol plus MK-801 showed a very similar day to day increase such that no statistical difference between the two groups occured. Thus, MK-801 was not able to block the day to day increase of catalepsy. On day 8, both groups received haloperidol plus saline an usual procedure for testing sensitization. This treatment did, as expected, not change catalepsy in the group having received the same treatment before. In the group having received haloperidol plus MK-801, the elimination of MK-801 (i.e. treatment with haloperidol plus saline) dramatically reduced the degree of catalepsy. Formally, according to the usual procedure of sensitization tests, it can be stated that previous treatment with MK-801 has prevented the development of sensitization and this conclusion would be in good accordance with the existing literature (for literature see Wise et al., 1996). However this would mean to ignore the day to day increase in catalepsy during day 1 to 7 in both groups.

Catalepsy is a behavioural state very different from motor stimulation, however very similar principles for the development of a day to day increase of hyperlocomotion have been found with morphine (Tzschentke and Schmidt, 1996) and with psychostimulants by Carlezon et al. (1995) and Wise et al. (1996). They report: "... not only were there progressive daily increases in bromocriptine-induced locomotion of MK-801-pretreated animals; the rate of sensitization in animals receiving the drug combination was identical to that

in animals receiving bromocriptine alone. In agreement with what was seen by others with other stimulants, the sensitized response was not apparent when the animals accustomed to the drug combination were tested in the absence of MK-801 (with bromocriptine alone). There was alone no evidence of a sensitized response when animals previously sensitized to bromocriptine alone were tested in the presence of MK-801 ..." (Wise et al., 1996).

Though the mechanisms underlying this phenomenon are far from beeing understood, it may be speculated that MK-801 itself acts as a very strong conditioned stimulus enhancing either the behavioural effects of morphine, psychomotor stimulants or the catalepsy inducing effects of the neuroleptic drug haloperidol.

Against this background, the view that MK-801, and possibly the other NMDA receptor-antagonists as well, block sensitization must be reconsidered. Also the procedure normally used for testing sensitization seems to be incomplete: It appears essential not only to test for sensitization in the absence of the NMDA receptor-antagonist, but also to consider the day to day increase in the absence and in the presence of an NMDA receptor blocker.

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